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THE MECHANISM OF RECOVERY IN ACUTE BACTERIAL PNEUMONIA *

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ALTHOUGH the treatment of acute bacterial pneumonia has been revolutionized in recent years by the advent of chemotherapy, the exact mechanism of recovery is not known. Pertinent to the problem are the following basic facts:

1. Most of the bacteria that cause the more common forms of acute pneumonia are encapsulated (pneumococcus, beta hemolytic streptococcus, Friedländer's bacillus, influenza bacillus, staphylococcus), and the presence of the capsules renders the organisms resistant to phagocytosis.[1] According to present concepts of immunology, fully encapsulated microörganisms can be phagocyted only in the presence of suitable opsonins.[2]

2. Sulfonamide drugs that are highly effective in the treatment of pneumococcal pneumonia act only as bacteriostatic agents in the concentrations attained by systemic therapy.[3] Likewise, penicillin, in the relatively low concentrations needed to cure pneumococcal pneumonia,[4, 5] will not kill pneumococci consistently in the presence of tissue.[6] † Thus the final destruction of the invading bacteria appears to depend upon the defenses of the host, and particularly upon phagocytosis.[7]

3. Intensive chemotherapy usually brings about recovery long before type specific antibody can be detected in the patient's blood serum.[8, 9] Histologic studies in experimental animals have demonstrated that phagocytosis takes place in the lung in the absence of both circulating and local antibody.[10]

From the above facts it is apparent that the most important question that remains unanswered concerns the mechanism whereby phagocytes in the lung destroy fully encapsulated bacteria in the absence of immune bodies.

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† When injected locally in sufficient concentration, penicillin is bactericidal.[6]

A. Pathogenesis of Pulmonary Lesion. During the past decade, a clearer understanding of the pathogenesis of acute bacterial pneumonia has been gained by histological analysis of experimental infections in laboratory animals.[11-15] The previously accepted concept that pneumococci causing pneumonia spread through the lung via the lymphatics [16-18] has been conclusively refuted,[14] and evidence has been presented from several laboratories that the invading organisms are carried through the lungs by infected edema fluid at the outer margin of the lesion.[11, 12, 13] Careful histological studies in both pneumococcal and Friedländer's bacillus pneumonia, indicate that the bacteria enter new alveoli through the pores of Cohn and via the bronchial tree.[13, 15] Robertson and Hamburger [19] have shown that interlobar spread in experimental pneumococcal pneumonia results from the passage of heavily infected edema fluid into the main bronchi of previously uninfected lobes.

Although the principal mechanism of spread of pneumonia through the lungs does not involve the lymphatics, it is clear that many of the invading organisms enter lymphatic channels and are thus carried to regional lymph nodes.[20-22] Bacteria that get by the lymph node barriers eventually reach the thoracic duct and are poured into the blood stream,[22, 23] causing bacteremia.

The pathogenesis of pleurisy and empyema is not clearly understood. The fact that the lymphatics at the periphery of the lung drain outward toward the pleura [24] suggests that the bacteria may enter the pleural space either via the lymphatics or by passing directly through the pleura from the underlying infected alveoli.

Only the outermost zone of the spreading pneumonic lesion is characterized by the presence of edema fluid. In the more central, older portions of the lesion the alveoli become filled with leukocytic exudate, and the edema fluid disappears.[13, 15] As the alveolar exudate becomes more concentrated, phagocytosis of the bacteria occurs, and frequently no bacteria can be found in the most central portions of the lesion. In such areas signs of resolution are present when the pneumonia is still advancing at the periphery.[13, 15] These histological features of the spreading pneumonic lesion as observed in experimental animals have also been described in the lungs of patients dying of pneumococcal pneumonia.[25]

Of particular interest is the fact that pneumococci are phagocyted and destroyed in the lungs of both animals and patients dying of the disease.[10, 13, 25] Since the pulmonary lesions contain large amounts of specific soluble substance, which combines with and neutralizes the opsonizing action of specific antibody,[26] and since under such conditions no free antibody can be demonstrated either in the blood serum or in the lungs,[9] it appears that leukocytes in the lung can phagocyte and destroy pneumococci in the absence of immune bodies, even in untreated fatal pneumonia.

B. Effect of Chemotherapy upon Lesion. The effect of chemotherapeutic agents upon the pulmonary lesions of both experimental pneumococcal and Friedländer's bacillus pneumonia has been studied in white rats.[6, 13]

Within a few hours after the start of treatment the bacteria in the outer edema zone of the lesions exhibit morphological changes indicative of bacteriostasis. Soon after the organisms cease multiplying, the edema zone disappears from the edge of the lesions, and phagocytic cells accumulate in the infected alveoli. Within 24 hours phagocytosis is noted even in the periphery of the now stationary lesions, and, in time, all of the bacteria are engulfed and destroyed by the phagocytic cells. After three to four days resolution of the pneumonic lesion becomes evident, with only a few large macrophages remaining in the previously infected alveoli. Repeated examinations have failed to reveal either circulating or local antibody at the time that the phagocytic reaction is most prominent in the lungs.[9, 27] Thus, direct histological studies of the recovery process during chemotherapy have shown that most of the bacteria in the lung are destroyed by phagocytic cells, and that this phagocytic reaction occurs in the absence of opsonins.

C. Non-Antibody Mechanism of Phagocytosis. When pneumococci are incubated with leukocytes in a fluid medium devoid of antibody, no phagocytosis takes place.[28] The leukocytes can be seen to push aside the organisms with which they come in contact during their migration through the fluid medium. If, however, mixtures of leukocytes and pneumococci in the same fluid medium are incubated upon various body tissues or upon rough inert materials such as filter paper, phagocytosis results. The manner in which the leukocytes successfully attack the encapsulated organisms on such surfaces is best shown by observing the process directly under the microscope in thin sections of formalin-fixed lung. In such preparations, the leukocytes can be seen to phagocyte the bacteria by trapping them against the tissue surfaces of the alveolar walls. Bacteria thus pinned against the tissue surfaces cannot escape phagocytosis.[28] Fully encapsulated strains of Friedländer's bacillus, pneumococcus type III, beta hemolytic streptococcus and staphylococcus have all been shown to be susceptible to surface phagocytosis.[29]

When sufficient numbers of leukocytes are present in the mixtures, the encapsulated bacteria are phagocyted not only by being trapped against tissue surfaces, but also by being caught between the surfaces of the phagocytic cells themselves.[30] The intercellular surface phagocytosis can be clearly demonstrated merely by concentrating the phagocyte-bacteria mixtures through centrifugation. When such concentrated mixtures are incubated, even in a test tube, marked phagocytosis results. Once taken into the cytoplasm of the phagocytes, the bacteria are promptly killed.[28, 31] Through these two forms of surface phagocytosis leukocytes may bring about destruction of encapsulated bacteria in the lung, in the complete absence of opsonins.*

D. Relation of Surface Phagocytosis to Recovery. The first stage of any acute inflammatory reaction is characterized by the outpouring of edema fluid into the inflamed area, and is promptly followed by a rapid accumulation of leukocytes. This familiar sequence of events occurs in acute bacterial

* Photomicrographs of the phagocytic phenomena described in this report have already been published.[28, 30, 31]

pneumonia, and during effective chemotherapy all of the invaded alveoli and bronchi eventually become packed with leukocytes.[6] The concentration of phagocytic cells in the consolidated areas of the lung makes it virtually impossible for bacteria to escape surface phagocytosis. Those organisms that are not phagocyted by being trapped against the tissue surfaces of the alveoli and bronchi are eventually pinned between the surfaces of two or more of the crowded leukocytes and are engulfed by the intercellular mechanism. Thus, the bacteriostatic action of the chemotherapeutic drug controls the spread of the lesion, and the leukocytes, through surface phagocytosis, destroy the bacteria that remain in the lung.

Since all of the invading organisms in acute bacterial pneumonia do not remain in the lung, those that enter the lymphatics and blood stream must eventually be accounted for in the process of recovery. There is indirect evidence that most of the organisms that escape from the lung are destroyed in the lymph nodes [32] and in such organs as the spleen, liver, and bone marrow.[33] The manner in which encapsulated bacteria are destroyed in these extra-pulmonary sites, in the absence of circulating immune bodies, is at present under investigation. It seems not unlikely that surface phagocytosis may operate in the sinusoids of the lymph nodes, liver, spleen, and bone marrow as well as in the lung.

The failure of phagocytic cells during systemic chemotherapy to sterilize areas of abscess formation, both within and outside the lung, deserves special comment. It is well known that patients with empyema and other suppurative complications of pneumonia are rarely cured by systemic chemotherapy alone.[34, 35] Studies of experimental Friedländer's bacillus pneumonia in rats have shown that complicating lung abscesses, that frequently develop during treatment, cannot be sterilized by intensive sulfonamide therapy.[31] The failure of leukocytes to rid abscesses of all bacteria would appear to be due to at least two factors. First, the absence of the normal tissue structures in abscessed areas deprives the leukocytes of the surfaces upon which they normally operate in intact tissue. Secondly, many of the leukocytes, particularly in the center of a large abscess, are either non-viable or so sluggish that they cannot phagocyte bacteria. Leukocytes deprived of oxygen quickly become non-motile and lose their phagocytic properties.[36] Since the only source of oxygen for leukocytes in an abscess is the intact capillaries at the periphery of the lesion, it is not surprising that the phagocytes in the central mass of pus fail to sterilize the lesion. To cure by chemotherapy such purulent complications as pneumococcal empyema, it is necessary, therefore, to inject large enough amounts of penicillin locally to obtain a bactericidal effect.[34]

It is not implied by the present analysis that antibody plays no rôle in the mechanism of recovery in pneumonia. It is known that antibody, when present in sufficient quantity, will agglutinate the bacteria in the outer edema zone of pneumonic lesions and will thus stop the spread of the infection.[12] Likewise, lesser amounts of antibody opsonize encapsulated bacteria and

greatly facilitate phagocytosis.[13, 28] Natural antibodies, however, are usually neutralized in the early stage of the acute infection,[37] and the production of acquired antibody by the host is a relatively slow process,[38] as is evidenced by the fact that complete recovery frequently takes place hours, and even days, before antibody can be demonstrated either at the site of the pneumonia or in the circulating blood.[9, 27] Surface phagocytosis, on the other hand, serves as an immediate defense reaction of the host against the invading bacteria.[28, 30, 31, 39] This more prompt form of phagocytic reaction which operates in the absence of antibody appears to account for the rapid destruction of bacteria that occurs in the lung as the result of effective chemotherapy.

Summary

Evidence is presented that, following adequate chemotherapy, prompt recovery from acute bacterial pneumonia depends in large measure upon the bactericidal effect of surface phagocytosis, a defense mechanism of the host that operates in the absence of immune bodies.

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BAL IN THE TREATMENT OF TOXICITY FROM GOLD *

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The value of therapy with gold salts in rheumatoid arthritis has been recognized increasingly as a useful addition to the therapeutic program in this disease. Unfortunately, toxic effects of varying degrees of severity have hindered wider employment of chrysotherapy and have often forced its discontinuance upon the appearance of the early signs of toxicity. The many types of toxic reactions resulting from chrysotherapy in rheumatoid arthritis will not be enumerated here since this subject has been discussed elsewhere.[1]

There has been a long felt need for some agent to counteract the toxic effects of gold therapy. Although various measures have been tried in the past, none proved effective.

In view of the reported observations on the effectiveness of British Anti-Lewisite (BAL) in the systemic treatment of arsenic and mercury poisoning,[2] it appeared to us that study of the possible effectiveness of BAL in the treatment of toxic reactions from gold should be undertaken. We have had occasion to observe the effect of the administration of BAL in five cases of toxic complications resulting from the use of gold in the treatment of rheumatoid arthritis. The striking benefit which was noted in one of these cases and the seemingly beneficial effect in three others warrants this preliminary report.

BAL (2,3-dimercaptopropanol) is a compound developed in England during the last war by Peters, Stocken, and Thompson [3] as a decontaminating and neutralizing agent against the arsenical blister gas, Lewisite. For this reason this new compound was named British Anti-Lewisite and has been marketed under the trade name of BAL.

It has been suggested that the toxic effect of arsenicals results from interference with cellular metabolism, since the heavy metal combines with SH groups in the tissues. BAL is presumed to exert its beneficial effect because of its affinity for the arsenical, combining with it before the metallic arsenic combines with the tissues, or by removal of the arsenic from the tissues after it has already combined.[4] It has also been intimated that the toxic effect of other heavy metals may be the result of a similar biologic action.[5]

Case Reports

Case 1. Mrs. A. G., a white woman 38 years of age, was first seen on August 21, 1946, with rheumatoid arthritis of two months' duration, involving both knees and ankles. There was evidence of synovial swelling of the knees and ankles; the tonsils

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From the Arthritis Department of St. Margaret Memorial and Montefiore Hospitals.

appeared to be infected. The sedimentation rate was accelerated to 24.5 mm. in 60 min. (Cutler method). Roentgenograms of both knees and the left ankle were normal.

In addition to systemic management and physiotherapy, treatment with aurothioglucose (Solganol B Oleosum) was instituted as follows:

August 24, 1946	.010 gm.	Total .010 gm.
August 31, 1946	.020 gm.	Total .030 gm.
September 7, 1946	.020 gm.	Total .050 gm.
September 14, 1946	.020 gm.	Total .070 gm.
September 21, 1946	.030 gm.	Total .100 gm.
September 29, 1946	.030 gm.	Total .130 gm.
October 12, 1946	.030 gm.	Total .160 gm.
October 24, 1946	.040 gm.	Total .200 gm.
November 2, 1946	.040 gm.	Total .240 gm.

By September 28, the joint pains and swelling had completely subsided. The sedimentation rate had improved to 20 mm. in 60 min. (Cutler method). On October 24, 1946, tonsillectomy was performed with uneventful healing at the operative site. On November 6, 1946, minute areas of ulceration appeared on the lower lip. Further administration of gold was discontinued. Nevertheless, by November 30, 1946, the patient had developed a severe ulcerative stomatitis and cheilitis involving especially the mucous membranes of both lips and the angles of the mouth, as well as a marked papulo-vesicular eruption of the skin around the mouth. The lips were swollen and injected, and the ulceration was so extensive that opening the mouth or eating induced bleeding from the ulcerated surface. On November 30, 1946, treatment with BAL was started, .150 gm. being given intramuscularly four times daily for two days, and .150 gm. twice daily, thereafter. Because of the appearance of nausea, it was necessary to reduce the dose after the fourth day to .100 gm. twice daily. After eight days of such treatment, during which time a total of 2.6 gm. of BAL had been administered, the stomatitis and surrounding area of dermatitis had cleared completely.

This case demonstrated the striking and dramatic recovery from severe stomatitis resulting from the administration of a fairly soluble gold salt preparation. BAL was started 24 days following onset of the toxic stomatitis which was increasing in severity until administration of BAL was instituted. Within eight days, during which 2.6 gm. of BAL had been given, the stomatitis cleared entirely.

Case 2. Mr. E. R. H., a white man 61 years of age, was first seen on March 19, 1946, with rheumatoid arthritis of seven months' duration, associated with bronchiectasis, diagnosed by bronchoscopy four years previously. Examination revealed a thin, pallid man. The proximal interphalangeal and metacarpophalangeal joints and both wrists presented typical rheumatoid changes. The right ankle was swollen and both knees presented synovial and capsular thickening. There was limitation of motion of both shoulders. The sedimentation rate was accelerated to 23 mm. in 60 min. (Cutler method). Roentgenograms of the right ankle, hands, and wrists revealed characteristic rheumatoid decalcification of the bones, but no narrowing of the joint spaces. The film of the chest indicated increased peribronchial infiltration.

In addition to the usual systemic measures and physiotherapy, treatment with aurothioglycolanilide (Lauron) was started. He received .150 gm. of Lauron from March 20 to April 5, 1946; thereafter .200 gm. to .300 gm. weekly until September 9, 1946, at which time a total of 3.150 gm. of Lauron had been administered. On September 23, 1946, he reported a transitory stomatitis of the roof of the mouth. Further gold was withheld for one month. On August 25, 1946, and again on September 7, 1946, .200 gm. of Lauron was administered, making a total of 3.550 gm. On Sep-

tember 25, 1946, a small anal excoriation with pruritus appeared; further administration of gold was discontinued. The ulceration persisted despite local therapy and on October 25, 1946, the patient reported a mild conjunctivitis and a solitary ulcer of the mouth. At this time the joints were generally improved. On November 22, 1946, scaliness of both upper eyelids was noted, and on December 13, 1946, he complained of pruritus and a scaly dermatitis of the scrotum and left hand.

Administration of BAL was started on December 20, 1946, with a dosage of .150 gm. intramuscularly four times daily. He had received a total of .900 gm. in a period of two days when administration of the drug was discontinued because of local soreness at the sites of injection. By January 3, 1947, the anal ulceration had improved and the scrotal dermatitis had completely subsided, but the conjunctivitis and scaly dermatitis of the eyelids, and left hand were unchanged. BAL was again administered from January 3, 1947, to January 10, 1947, with a dosage of .150 gm. twice daily for an additional total of 2.4 gm., following which the residual dermatitis of the left hand, the conjunctivitis, and the anal ulceration had entirely cleared.

In this instance involvement of the skin and mucous membranes of the eyes, mouth, and arms resulting from the administration of a slowly absorbed gold salt preparation was neither extensive nor severe; however, it did not respond to local therapy. BAL was started approximately two months after the onset of the reaction to gold. Complete subsidence of the skin and mucosal lesions ensued following the administration of 3.30 gm. of BAL.

Case 3. Mrs. E. C., a white woman 67 years of age, was first seen on January 27, 1945, because of pains in the shoulders, arms, hips, and knees of one year's duration. Examination revealed a pallid, sick woman with generalized joint stiffness and periarticular soft tissue swelling of many joints typical of rheumatoid arthritis. This was superimposed upon a preëxisting degenerative arthritis. There was also evidence of calcareous aortic stenosis and insufficiency, but without myocardial decompensation. The blood count showed a marked hypochromic anemia, and the sedimentation rate was accelerated to 28 mm. in 60 min. (Cutler method). Roentgenograms of the spine and the sacro-iliac joints showed changes typical of an advanced Marie-Strumpell spondylitis; roentgen-rays of the left shoulder and hips were negative.

In addition to systemic management and physiotherapy, aurothioglycolanilide (Lauron) was administered, the initial dose being .050 gm. with gradual increase in the dose until a maximum of .300 gm. to .400 gm. was given weekly. This was continued from February 6, 1945, until September 18, 1945, at which time a total of 5.950 gm. had been given. Although there was evidence of moderate improvement in the arthritis, the sedimentation rate remained accelerated, being 25.5 mm. in 60 min. (Cutler method).

One week after administration of gold was discontinued, the patient developed a generalized dermatitis which rapidly progressed into a severe generalized exfoliative dermatitis. Except for the face and gluteal regions, the entire skin surface was markedly erythematous, itchy, and scaly with many fissures and exudation of serum. Soothing applications were applied to the skin, but the dermatitis remained practically unchanged for nearly a year. On August 11, 1946, the patient was admitted to the Montefiore Hospital because of mild congestive failure which was readily controlled by digitalis.

Although by September 22, 1946, the dermatitis was slightly improved, the patient was readmitted to the Montefiore Hospital for treatment with BAL. On September 23, 1946, .150 gm. of BAL was administered every four hours for 12 doses, followed by .100 gm. to .150 gm. twice daily. By September 28, five days following the in-

stitution of treatment with BAL, after a total of 3.0 gm. had been administered, improvement of the dermatitis was clearly perceptible, the most striking change being marked reduction in the degree of erythema and fissuring of the skin, with consequent diminution in the amount of oozing of serum. We could observe no change in the tendency to desquamation. Subsequent administration of an additional 2.1 gm. of BAL from September 28 to October 8, resulted in no further improvement of the dermatitis.

This case of severe generalized exfoliative dermatitis of one year's duration resulting from treatment with a slowly absorbed gold salt was intractable to all previous therapy. With the administration of 3.0 gm. of BAL over a period of five days, improvement in the dermatitis, but not complete subsidence, occurred, evidenced by decrease in the degree of erythema and cessation of oozing of serum. Administration of additional BAL did not induce any further improvement.

Case 4. Mrs. G. McG., a white woman 42 years of age, was first seen on September 31, 1942, with an early rheumatoid arthritis. There was puffiness and stiffness of the finger joints, hypochromic anemia, and infected tonsils. The sedimentation rate was 18.5 mm. in 60 min. (Cutler method). Roentgenograms of both hands and knees were negative.

In addition to systemic measures and tonsillectomy, treatment with a soluble gold salt was instituted. From September 14, 1942, to October 26, 1942, she received a total of 335 gm. of aurothiomalate (Myochrysine) with no untoward reaction. There was some improvement both generally and in the joints.

She was not seen again until March 23, 1945, at which time there was evidence of marked reactivation of the arthritis. There were periarticular swelling and stiffness of the hands and knees, stiffness of the shoulders, many large subcutaneous rheumatic nodules, left axillary adenopathy, and hypochromic anemia. Biopsy of the left deltoid muscle showed on histological section islands of mononuclear cell infiltration, interstitial fibrosis and cloudy swelling of muscle fibers, such as have been described to occur in rheumatoid arthritis.[6] The sedimentation rate was 20 mm. in 60 min. (Cutler method). Systemic therapy and gold were resumed. This time aurothioglycolanilide (Lauron) was given, starting with .025 gm., with gradual increase in the dose until a maximum of .400 gm. was administered weekly. The latter dose was continued until August 6, 1945, at which time a total of 6.080 gm. of Lauron had been given. On August 13, 1945, slight pruritus and scaliness appeared involving the skin behind both ears. There was gradual progression of the dermatitis with involvement of the axillae and groins, then a more generalized erythema and scaling, and by January 30, 1946, the patient presented a severe exfoliative dermatitis with erythema, desquamation and oozing of serum. There was also evidence of a nephrosis; marked albuminuria with an occasional hyaline cast, but without cellular elements in the urinary sediment. The blood non-protein nitrogen was 31 mg. per cent; serum protein 5.36 gm. per cent; serum albumin 2.17 gm. per cent; and serum globulin 2.19 gm. per cent.

Except for minor fluctuations, the dermatitis remained more or less the same for a year. However, with general and local measures of treatment and repeated blood and plasma infusions, the dermatitis had cleared by August 29, 1946, leaving only residual pigmented areas. The nephrosis cleared entirely, leaving no apparent residue. The arthritis was completely arrested, all the subjective and objective manifestations having disappeared. Roentgenograms of both gluteal areas at this time showed remaining deposits of the heavy metal.

On October 22, 1946, there was a fresh mild recurrence of the gold dermatitis. Treatment with BAL was then started with a dosage of .150 gm. intramuscularly every four hours for two days, followed by .150 gm. twice daily for 10 days. At the end of this time, after approximately 4.8 gm. of BAL had been administered, the patient reported that the dermatitis was again largely cleared. She was seen again on January 24, 1947, at which time the skin rash was completely gone. The patient was still entirely free of subjective and objective manifestations of rheumatoid arthritis. The blood count, sedimentation rate, and urinalysis were entirely normal.

This patient developed a severe generalized exfoliative dermatitis and nephrosis following treatment with a slowly absorbed gold salt (Lauron). After one year's duration, both the dermatitis and nephrosis subsided completely. A mild recurrence of the dermatitis two months later was treated with 4.8 gm. of BAL, administered over a period of 10 days; complete clearing of the dermatitis ensued.

Case 5. Mrs. M. W., a white woman 59 years of age, was first seen on March 27, 1946, with rheumatoid arthritis of 20 years' duration. Examination revealed a pallid woman in considerable distress from arthritic pain. The joints showed changes typical of an advanced chronic rheumatoid arthritis. There was synovial and capsular thickening of the proximal interphalangeal joints of both hands and wrists, with flexion contractures and ulnar deviation of the fingers. Motion at both elbows was markedly limited, the knees and ankles were swollen, and there was considerable limitation in the range of motion in these joints. The sedimentation rate was accelerated to 25 mm. in 60 min. (Cutler method). Roentgenograms of both hands and knees showed destructive joint changes characteristic of an advanced rheumatoid arthritis.

In addition to the usual systemic measures and physiotherapy, treatment with aurothioglycolanilide (Lauron) was started, the initial dose being .050 gm., with gradual increase in the dose to a maximum of .200 gm. weekly. This was continued until August 20, 1946, at which time 4.350 gm. had been given, following which .200 gm. was administered every other week until December 9, 1946, until a total of 5.950 gm. had been given. At this time there was remarkable improvement in the arthritis, estimated to equal approximately 75 per cent. The sedimentation rate had likewise improved to 16.5 mm. in 60 min. (Cutler method). On December 23, 1946, several small pruritic scaly patches were noted on the skin of the anterior chest and left thigh. Administration of gold was discontinued. Within a period of four weeks, however, the dermatitis became more marked, consisting of scaly patches over the trunk and right upper eyelid. At no time, however, was the skin reaction very distressing or disabling.

Administration of BAL was started on January 20, 1947, with a dosage of .150 gm. four times daily for two days, followed by .150 gm. once to twice daily, thereafter, until approximately 3.0 gm. of BAL had been administered. When the patient was seen again on January 27, 1947, and on February 25, 1947, there was only slight improvement in the dermatitis.

The dermatitis in this case followed the administration of a slowly absorbed gold salt (Lauron). Although the skin lesions were not extensive and BAL was started 28 days following the onset of the dermatitis, there was little apparent benefit from the use of BAL.

Discussion

The therapeutic response to administration of BAL in the first case of our series demonstrated vividly the prompt resolution of a severe gold stomatitis induced by a relatively soluble and quickly absorbed preparation of gold, namely aurothioglucose (Solganol B Oleosum). It should be pointed out that the total amount of gold administered was relatively small and that it was given in small divided doses. Although we cannot discuss in detail the possible mechanisms of gold intoxication, it is our impression that an inherent idiosyncrasy is probably responsible to a large extent, especially when toxicity appears after relatively small amounts of the drug have been given. In any event, in the light of our past experience with similar cases, a stomatitis such as this patient (Case 1) presented would have lasted many months. With BAL resolution of the stomatitis was so prompt and complete that we can have no doubt of the value of the treatment. It should be emphasized, however, that the gold salt administered in this case was not only a relatively soluble and readily absorbed preparation, but that treatment with BAL was instituted within a relatively short period of time (within 24 days) after appearance of the first signs of toxicity.

In the second case the toxic effects, consisting of both skin and mucous membrane lesions, followed the administration of aurothioglycolanilide (Lauron), a much less soluble and more slowly absorbed gold salt. The conjunctivitis and anal ulceration persisted without any substantial improvement for approximately 10 weeks. Following the administration of BAL the mucosal lesions, as well as the dermatitis, cleared completely within less than a month. Although the possibility of spontaneous subsidence of these lesions cannot be entirely excluded, their persistence until BAL was administered and their prompt disappearance following the exhibition of this drug, makes us feel that BAL was instrumental in reversing the toxic effect.

In the third patient (Case 3) we feel that the use of BAL was effective in inducing some healing of the more acute manifestations of a generalized exfoliative dermatitis resulting from treatment with Lauron. The residual lichenification and scaling may have been the result of long standing damage to the skin. In the fourth patient (Case 4) recurrence of the dermatitis after apparent recovery may be presumed to have been caused by release of gold from depots at the sites of injection in the gluteal regions or by gold which had been stored elsewhere in the body. In any case, the prompt recovery from the reactivated dermatitis, in contrast with the protracted course of the dermatitis during the initial phase of the toxic reaction, may be related to the prompt administration of BAL. However, in view of the subsidence of the previous dermatitis, we cannot be sure that spontaneous recovery might not have occurred.

Although the dermatitis resulting from Lauron in Case 5 was mild in character and BAL was started within a relatively short period of time after the appearance of the skin reaction, treatment with BAL was ineffective.

We can offer no certain explanation for this disappointing result. Whether the persistence of the dermatitis was related to continued active absorption of gold from the injected sites can only be conjectured. If that is true, it is possible that the partial improvement noted in the long standing cases of dermatitis caused by Lauron (Cases 3 and 4) was due to the fact that the residual depots of gold were partially encapsulated by fibrous tissue so that further absorption was precluded or at least markedly slowed. It appears, therefore, that the striking effectiveness of BAL in the case of toxicity from aurothioglucose might have been the result of both the early administration of BAL and the solubility and rapidity of absorption of the gold salt preparation, whereas the partial effectiveness or total ineffectiveness of BAL in the other instances treated, caused by Lauron, were related to the less soluble quality of the drug or the duration of the dermatitis, or both.

It should be pointed out that the incidence of intoxication from the two preparations of gold mentioned in this small series treated with BAL does not reflect the actual relative toxicity of these two preparations.

Although we have been favorably impressed with the response to the administration of BAL in the first two cases cited and feel that BAL may have had some ameliorating effect in the third and fourth cases as well, we realize that the number of cases available for this report is too small to warrant final conclusions as to the effectiveness of BAL in the treatment of gold toxicity. The results do suggest, however, that in BAL we may have an agent that may prove valuable in the treatment of some of the toxic complications resulting from the therapeutic administration of gold. Further trial of BAL is certainly warranted in such instances.

Summary and Conclusions

Five cases of toxic reactions resulting from the therapeutic administration of gold in rheumatoid arthritis were treated with BAL (2,3-dimercaptopropanol).

In two cases BAL appeared to be of distinct benefit. In one of these a severe stomatitis from the administration of aurothioglucose (Solganol B Oleosum) responded dramatically. In the other patient, a mild conjunctivitis, anal ulceration and dermatitis resulting from aurothioglycolanilide (Lauron) cleared entirely.

In two cases of long standing generalized exfoliative dermatitis resulting from aurothioglycolanilide (Lauron) BAL appeared to have induced amelioration of the dermatitis.

In the fifth case, a mild dermatitis resulting from the administration of aurothioglycolanilide (Lauron), no appreciable benefit from the use of BAL could be noted.

Early use of BAL in the treatment of toxic effects resulting from the administration of gold appears to be of value.

Since the writing of this paper several publications on the use of BAL for gold intoxication have appeared.[7]

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THE ORIGIN AND THE PHYSIOLOGY OF HEPARIN: THE SPECIFIC THERAPY IN THROMBOSIS *

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The Chemistry of Heparin. A few years after the discovery of heparin by McLean [1] in 1916, while working under Howell, the latter author found that heparin gives a color reaction for uronic acids.[2] When the Toronto School at the Connaught Laboratories, in 1933,[3] had solved the problem of preparing larger quantities of heparin directly from fresh organs, I succeeded, in 1935,[4] in identifying heparin, as a mucopolysaccharide resembling the chondroitin sulfuric acid of the cartilage. The strongest heparin samples were found to contain about 26 per cent of a uronic acid and about 23 per cent of glucosamine, these components together making up about 90 per cent of the organic skeleton of heparin. On this occasion, the observation was made that heparin contains ester sulfuric acid, and surprisingly enough, not only one group to each disaccharide unit, as in chondroitin sulfuric acid, but three groups making up not less than 45 per cent of the weight of the free acid. Opinion is now unanimous with regard to these facts.

The uronic acid in heparin is claimed to be glucuronic acid.[5] Opinions still differ as to whether heparin contains an acetyl group or not. All the other known polysaccharides containing an amino sugar are acetylated at the amino group. In heparin also there is no free NH_2-group. Acetic acid, however, cannot be obtained from heparin by applying the ordinary methods of analysis, except for a small quantity, 10 to 15 per cent of the calculated amount—which could possibly be derived from impurities in the heparin preparations. The accompanying polysaccharides namely, split off acetic acid easily, and heparin is very difficult to purify. It is, in fact, doubtful whether any homogeneous pure samples of heparin have ever been prepared.

The whole discussion on the acetyl content of heparin has so far been founded on erroneous analytical data as well from our laboratory as from those of other workers.

There are thus many details as to the chemistry of heparin which are still uncertain. It will also be necessary to find out whether heparin is a definite chemical compound or whether it is a mixture of di- and trisulfuric acid esters of one and the same polysaccharide having a composition similar to that of Karl Meyer's hyaluronic acid. All kinds of polysaccharides acquire anticoagulant properties if thoroughly esterified with sulfuric acid.[6, 7, 8]

The Mechanism of Action of Heparin. The physico-chemical properties of heparin are quite unique. It has a high molecular weight and carries an

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exceptionally strong electric charge, apparently the strongest of all the organic compounds of the animal body. The strongest preparations, which contain 13.6 per cent of sulfur in the sodium salt, consist of no less than 45 per cent of sulfuric acid, really a peculiar product of synthesis in the living organism. The strongest compounds of a similar nature hitherto known, the nucleic acids, contain only 25 per cent of phosphoric acid. The high content of ester sulfuric acid is the most outstanding feature in the structure of heparin. *The sulfuric acid is as good a prosthetic group as any.* There are no other known reactive groups. All chemical findings therefore point in the direction that the anticoagulant activity is exerted through the electric charges of the high molecular polysaccharide.[9] The same is the case with the physiological findings.

Heparin has a multiple effect, acting not only on the components of the coagulation system, on the thrombin, the prothrombin, and the thrombokinase, but also on many other systems. It neutralizes the serum complement interfering in the Wassermann reaction. It reduces the isoagglutinin titer of the serum and it acts on different enzymes, preventing their action. In larger concentration (1 mg. per ml.) it also acts on the plasma proteins, strongly influencing the sedimentation rate of the red blood corpuscles. This multiplicity in its action can most easily be explained as a physico-chemical action of the acidic polysaccharide on the different proteins concerned. It is also known that the interaction between heparin and thrombin is reversible and very loose, it being reversed by adding an excess of thrombokinase.

It is known that lecithin and nucleic acids are capable of influencing the electric charge of proteins, moving their isoelectric point to the acidic side. Anionic i.e. acidic detergents, like dodecyl sulfate, act upon proteins even on the alkaline side of the isoelectric range, where the proteins are acids, acting upon the basic charges still present in the anionic protein. *It is a most interesting fact that the very few synthetic organic chemicals we knew of earlier, which acted directly as anticoagulants, such as Liquoid Roche and some diazo dyes, were all sulfonic esters of high molecular compounds.* All kinds of polysaccharides acquire anticoagulant properties if thoroughly esterified with sulfuric acid. Nature, in synthesizing heparin, has applied the same principle, and has done it in an excellent way, *the product being not only highly active but also non-toxic.* Even the polysaccharide polysulfuric esters so far prepared by various authors have more or less toxic properties.

The most convincing proof for the action mechanism of heparin was obtained through the finding of Chargaff and Olson[10] (1938) that protamine instantaneously abolishes the heparin effect in vitro and in vivo. Its electric charge neutralizes the negative electric charge of heparin.

Protamine sulfate, 50 to 100 mg., can be injected intravenously in man in 1 per cent sterile solution. The coagulation time of the blood is thereby instantaneously brought down to normal.

It has recently been found by Seegers that the prothrombin cannot be

absorbed on magnesium hydroxide if heparin is present. Evidently the physico-chemical state of the prothrombin is altered.

A physico-chemical mechanism of action seems therefore to be the most probable.

There are facts, however, not so easy to explain. Thus Jaques [11] found dog heparin to have a two and one-half times stronger anti-coagulant effect than the same amount of ox heparin, whereas pig and sheep heparins are much weaker. They all have the same content of ester sulfuric acid. His findings have later been fully confirmed.

The osmotic properties of heparin show a very interesting feature. In spite of a strong ionic dissociation, it exerts an extremely low osmotic pressure in aqueous solution.

This is the same phenomenon which E. Hammarsten [12] (1924) studied in another strongly acidic compound of high-molecular weight, the thymonucleic acid of cell nuclei. Both these substances, heparin and the thymonucleic acid, in aqueous solution show only a fraction of the osmotic pressure which the degree of ionization would lead one to expect. The salts of heparin exert less than a tenth of the calculated osmotic pressure. The phenomenon involves an interesting protective mechanism which nature has developed to avoid high osmotic pressure and the resulting displacement of fluid when compounds with a high electric charge are deposited in cells. Otherwise, no nucleic acid could be stored in the cell nuclei, nor any heparin in the heparin-producing cells. The nuclei and the cells would be disrupted by the water entering them from outside in order to establish osmotic equilibrium on both sides of the nuclear and cellular membrane respectively. The sodium or potassium ions bound to the high molecular negative complexes of heparin and the nucleic acids respectively do not exert any osmotic pressure although they occur as ions. They have disappeared "im Lebensraum des grossen Molekuls." When someone disappears into the living space of the more powerful ones, having an opposite charge, he has, indeed, very little say. It is not without interest to observe how Nature, when life's conditions so demand, has put out of function one of the most fundamental natural laws, that of the osmotic pressure of salt solution.

This lack of osmotic pressure makes heparin very useful in blood analysis, because it does not cause shrinkage of the red blood corpuscles. It is the only anticoagulant to be used in hematocrit determinations. A concentrated 5 per cent solution of heparin can also, without any drawbacks, be injected undiluted into the blood.

Heparin and the Ehrlich Mast Cells. The unusual physico-chemical properties of heparin show another peculiarity. Heparin gives an extraordinarily strong metachromasia, a purple violet staining with certain blue basic dyes.

At a time when the sulfur content of heparin was denied by several authors, it was possible to demonstrate that it gave an exceedingly strong

violet metachromatic reaction with toluidine blue,[13] a reaction which a Belgian histologist, Lison,[14] had shown in 1935 to be given only by high molecular esters of sulfuric acid. The metachromasia of the cartilage is due to the chondroitin sulfuric acid. Heparin gives a 100 times stronger metachromasia than does this acid. By means of this reaction, we were able to demonstrate in 1937, together with Holmgren and Wilander,[15, 16] that heparin is produced by the mast cells of Ehrlich.

In 1933 Quensel,[17] Professor Emeritus of Pathology at Uppsala in Sweden, published a paper on these cells. Summarizing the results of a study of human material, he concluded that he—like Staemmler before him—regarded the mast cells as unicellular glands of the connective tissue.

He found the topography of the mast cells very characteristic, with an accumulation close to the walls of the smallest blood vessels and the capillaries. The perivascular position is so regular and consistent that it is an essential feature of the topography of the mast cells, and cannot be regarded as accidental. "This appearance is so consistent that it must have some relation to the hitherto unknown function of the mast cells." Four years later we were able to explain this relationship.

The mast cells, because of their position around capillaries and the small blood vessels without a muscular coat, are able to void their granular contents into the peripheral tissue juices, or almost directly into the blood stream, a state of affairs which indicates that these cells—and with them the heparin—may have a physiological function to fulfill. The mast cells evidently form a hormonal system, with the cells widely distributed around the capillaries in the body.

The close connection between the mast cells and the blood vessels has recently been demonstrated in different ways. We were also previously aware that the mast cells follow the capillaries, that neoplastic and inflammatory tissues rich in capillaries are also rich in mast cells. Recently, Holmgren—who did the histological part of our common work on the mast cells—has shown that there is a steady and very considerable decrease during the course of life. This reduction in number of the mast cells corresponds to the reduction of the capillaries with increasing age.

A most interesting increase in the mast cell content of the tissues was observed in the victims of Hiroshima. A general bleeding tendency was observed in the survivors as a consequence of the irradiation. Histologists stated that there was a general increase of the mast cells in the tissues of the victims. A similar condition with hyperheparinemia has recently been produced by Garrott Allen[18] in Chicago through roentgen-ray irradiation of dogs.

We also have a disease, urticaria pigmentosa, with multiple petechial hemorrhages in the skin in which the pathologists long ago stated that there are abnormal local accumulations of mast cells in the skin.

Recently, Robert Ehrstrom, in Finland, suggested that these cells should

be named heparinocytes, which is of course a nomination much more convenient than the German name "Mastzellen."

Before leaving the discussion about the mast cells, which we now know produce heparin, I feel that we should pay a tribute to Ehrlich for his introduction of the specific stains which he himself used so successfully. With them, he succeeded in staining the granules of the leukocytes, different bacteria and also—in using methyl violet and basic saffranine—to separate the mast cells from Waldeyer's plasma cells. When he did this, 70 years ago, he could hardly have anticipated that his specific stains—in this case toluidine blue—would in due time enable us to demonstrate the natural anticoagulant at the site of its formation.

Heparin in Thrombosis. For the medical profession the most important question is to what extent this natural anticoagulant can be used in thrombosis. As late as 1934 the great German clinician, Morawitz, confessed that we were at that time as helpless against thrombosis as fifty years ago, and that real progress in that field was not to be expected "unless we are able to influence not only the mechanical factors but also the fundamental processes of the blood which induce coagulation and thrombosis." In the meantime, Homans and his associates [19] have shown that a mechanical procedure, the venous interruption, the ligation of the femoral vein, is quite effective in combating pulmonary embolism. The specific treatment by influencing the coagulation mechanism is now also at our disposal. The coagulation tendency of the blood can be controlled in vivo. This can be achieved not only by means of heparin, the physiological anticoagulant of the body itself, but also thanks to the excellent work of Dr. Link [20] and his associates in this country, by eliminating the prothrombin production by means of dicumarol. These anticoagulants have now proved effective both for the prevention and treatment of thrombosis and pulmonary embolism.

Simultaneously and independently Crafoord [21] in Sweden and Gordon Murray [22] in Canada showed during 1935–1942 that thrombosis can be prevented if heparin is given post-operatively in sufficient amounts, 250 to 325 mg. a day, until the patient is out of bed. About 800 cases were reported from Sweden and half the number from Canada. Practically no thrombo-embolic complications occurred, although a frequency of 2 to 4 per cent could have been expected. Similar good results have been reported in using dicumarol, which has been given to more than 1000 cases prophylactically at the Mayo Clinic [23] and to 1500 cases at Lund in Sweden.[24]

The cost of the treatment and the labor involved, however, preclude a general application of the prophylaxis with anticoagulants. There is also a pronounced bleeding tendency from the field of operation. In spite of these drawbacks, *anticoagulants are to be given prophylactically after operations or childbirth where there have been single or recurrent attacks of thrombosis in the history of the patient.*

We already have a quite extensive experience with the use of heparin

alone or in conjunction with dicumarol in thrombosis. Already in their first papers on the use of heparin in man, Murray and Best [25] in 1938, and Murray and MacKenzie [26] in 1939, reported on a number of cases of spontaneous thrombo-phlebitis and pulmonary embolism treated with heparin. The acute symptoms disappeared in a surprisingly short time. There was no spreading to the other leg, nor were there any recurrences of pulmonary embolism. The anticoagulant therapy was combined with free active movements.

In Sweden, Gunnar Bauer has shown particular interest in this question. In 1940,[27] he found that an incipient thrombosis in the lower part of the leg was checked in its growth by heparin treatment, combined with free movements and early ambulation. The patients could leave the bed in four to six days.

Anticoagulant therapy is at present routine in Sweden in cases of ordinary leg thrombosis and pulmonary embolism. In some clinics only heparin is used, in most of the clinics it is given in conjunction with dicumarol.

Heparin has been given in three or four daily intravenous injections, 100 to 125 or 150 mg. each time. Usually 350 to 450 mg. of a sodium salt with 80 Toronto units per milligram are given a day. The effect is not controlled by any blood analyses except for special cases, e.g. elderly persons with impaired renal function. Consequently heparin treatment can be given at any hospital, even the smallest ones, and if necessary, at the home of the patient. The bleeding tendency is not very pronounced.

Bauer [28] himself has reported on 260 cases treated with heparin during the last six years, and in 1945, Zilliacus [29] collected 600 cases of thrombosis or pulmonary embolism from 20 different clinics, most of them treated with heparin.

Summarizing the results, it can be said that the thrombotic process is effectively checked, if the anticoagulants are given in an adequate dose. The recumbency time is shortened to one week or less from six weeks. The mortality is practically nil, from being earlier 5 per cent in obstetric cases and 20 per cent in surgical and medical cases. The effect of the treatment is so consistent that it is necessary to search for an error in the treatment or to consider another diagnosis if the patient does not respond favorably to the treatment.

As to the results of the anticoagulant therapy, there is one more detail of special importance. The sequelae usually following thrombosis, swollen legs, indurations, pain, eczema and ulcers, can be prevented if the thrombosis is checked early while still confined to the calf. This detail has been particularly stressed by Bauer.[30] In a study of 1300 cases of leg ulcers, Birger,* in Sweden, recently found the ulcers to be caused by a previous thrombosis in not less than 40 per cent of the cases. Likewise, Zilliacus * last year made a follow-up examination of 680 patients, who had suffered from a thrombosis

* Unpublished communication.

6 to 14 years earlier. Ninety per cent of them had more or less severe troubles with their legs; more than 50 per cent had chronic induration and eczema of the leg; 20 per cent had leg ulcers, chronic or recurrent; and an equal number had similar changes in the other leg. One in 10 of the patients had become completely disabled, incapable of any work.

The cases treated with heparin in an early stage of the disease have, on follow-up examination, shown quite a different picture. Where the process had been confined to the calf, the leg had usually remained normal. Much suffering and social disablement could consequently be avoided if the cases with spontaneous deep venous leg thrombosis were diagnosed in time and immediately given an adequate therapy. At least during the first days is heparin to be given.

The use of the anticoagulants is, however, not confined to the treatment of leg thrombosis and pulmonary embolism. Its use in other thrombotic conditions and in vascular surgery has been discussed in a recent monograph.[31]

Most interesting observations have recently been made as to the cause of some non-virus pneumonias with a protracted course and resistant to antibiotics. Here heparin and dicumarol often have a quite specific effect. There may be a rise in temperature lasting for weeks, blood stringed sputum and diffuse symptoms from the lungs, resistant to sulfa and penicillin therapy. As soon as heparin and dicumarol are given, recovery follows within a few days.* Latent thrombi, e.g. in the pelvic veins giving pulmonary infarctions, are far more common than suspected in these cases. The anticoagulant therapy not only clears up the diagnosis but also protects the patients from recurrent pulmonary embolisms.

The possibility of checking the fibrin formation by means of anticoagulants will certainly be extensively studied in different disease conditions where it is desirable to prevent further fibrin formation in the capillaries and their vicinity, e.g. in allergic and acute rheumatic conditions. This is demonstrated in the following case.* A woman who had received repeated blood transfusions developed Rh-immunization. After a renewed transfusion she manifested a hemolytic shock, with oliguria developing overnight into anuria. The following day she got 125 mg. of heparin three times. Within two hours after the first injection she excreted 400 ml. of urine. In the next 12 hours the excretion was 1200 ml.

Our results in applying anticoagulants, mainly heparin in thrombosis in Sweden during the last six years are clearly demonstrated in the following three tables. Table 1 comprises the material of Bauer. Table 2 shows the change in mortality following the introduction of the anticoagulant therapy in different clinics during 1940 to 1944 and table 3 shows the 900 cases of deep venous thrombosis or pulmonary embolism, treated mostly with heparin and some of them with heparin and dicumarol, reported by Bauer and Zilliacus together.

* S. Kallner: Unpublished communication.

TABLE I

Heparin Treatment of Thrombosis and Pulmonary Embolism at the Mariestad Hospital, Sweden, 1940–1946

	No Treatment 1929–1938	Heparin Treatment October 1, 1940–September 30, 1946
Number of patients admitted	25,628	20,002
Number of thrombosis cases	264	258*
Fatal embolism	47	3
Mortality in thrombosis cases	18 p.c.	1.1 p.c.
Average duration of stay in bed	40 days	4.6 days
Disabling after-effects	Serious	None or very slight

* 104 patients were admitted to the Mariestad Hospital on account of thrombosis.

TABLE II

Series of Thrombotic Cases Treated with Anticoagulants, mainly Heparin, during 1940–1944

	Without Anticoagulants		With Anticoagulants	
	Cases	Deaths	Cases	Deaths
Med. Clinic A	16	9	22	0
Surg. Clinic A	71	17		
Surg. Clinic B	41	5	26	0
Surg. Clinic C			74	0
Surg. Clinic D	33	11	31	1
	161	42	153	1

TABLE III

Mortality in Cases of Thrombosis or Pulmonary Infarction (Bauer, Zilliacus)

	Cases	Deaths	Per cent
Conservative treatment	543	88	16
Heparin	769 } 900	5 } 6	0.67
Dicumarol	131 }	1 }	

To these 900 carefully controlled cases of thrombosis or pulmonary embolism from Sweden can be added 371 cases of thrombophlebitis of the deep veins and 149 cases of pulmonary embolism, in total 520 cases treated with heparin in Canada and reported by Murray in 1946,[32] among which no fatal cases occurred.

The results obtained in using heparin have been successfully supplemented by the experiences in using dicumarol as reported from the Mayo Clinic.[33, 34]

The results in using anticoagulant therapy are as striking as any hitherto reported following the introduction of a specific therapy in medicine.

Since this very month is the centenary of the introduction by Semmelweis at the Maternity Clinic of the Allgemeines Krankenhaus in Vienna of his new principle for the prevention of death in puerperal fever, I take the opportunity

of reminding you about this milestone in medicine. In May 1847, he prescribed ordinary washing of the hands, followed by rinsing with chlorinated water, in order to prevent the transfer of the contagion or the miasma which he believed caused puerperal fever. His results were as follows:

TABLE IV

Years	Patients	Deaths Per cent
1846	3,354	13.6
1847	3,375	5.2
1848	3,356	1.3

Mutatis mutandis, we have achieved equally good results as Semmelweis did in our efforts to treat another serious complication following childbirth and operations. We are now evidently able to control the course of the thrombo-embolic disease, not only by mechanical means but also as Morawitz hoped, by checking the fundamental processes of the blood which induce coagulation and thrombosis.

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THE USE OF DICUMAROL AS AN ANTICOAGULANT: EXPERIENCE IN 2,307 CASES *

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Six years have elapsed since the first report on the clinical use of dicumarol.[1] Since that time there have been a number of clinical reports by ourselves and others. The literature has been reviewed previously.[2, 3] It is the purpose of this presentation to consider this new therapeutic tool in the light of six years' experience.

Dicumarol is a pure chemical compound which may be recovered from spoiled sweet clover and which has been prepared synthetically. The discovery that it is the agent which causes spoiled sweet clover disease of animals which is characterized by hemorrhage, the determination of its chemical formula, the synthesis of it and other studies by Link and his associates mark an epoch in research which is admirably presented in the Harvey lectures for 1943–1944.[4] Dicumarol impairs coagulation of the blood, in vivo, by depressing the values for prothrombin. When used clinically it has no other significant effect, except that hemorrhage may result when the concentration of prothrombin in the blood is diminished too greatly. Dicumarol is not an ideal anticoagulant because its effect is delayed for one to two days after oral administration, because its effect persists for several days after discontinuance of administration and because judicious use requires the services of skilled and experienced laboratory personnel. Heparin, the only other anticoagulant available for clinical use, has the advantage of quick action (within a few minutes after intravenous injection) and quick cessation of action (about three hours after injection). A further advantage is that it can be satisfactorily administered without "laboratory control." The disadvantages of use of heparin are the relatively great cost and the need for parenteral administration.

Heparin and dicumarol are not competitors for clinical use; the use of one complements the use of the other. In many instances they should be used together. Heparin should always be used when an anticoagulant effect is needed quickly and when reliable laboratory determination of the value for prothrombin in the blood is not available. Although it may be given by continuous administration, the intravenous injection of 50 mg. of heparin (5 c.c. of solution) every four hours has been satisfactory for clinical use. Dicumarol should be used whenever an anticoagulant effect is needed over a

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period of days, weeks, months or years, provided that there are available reliable determinations of the value for prothrombin in the blood. When both a rapid and a prolonged effect of an anticoagulant are desired, heparin and dicumarol should be administered simultaneously; administration of heparin should be discontinued when dicumarol has produced a satisfactory effect on prothrombin.*

The Dosage of Dicumarol

The amount of dicumarol to be used depends entirely on the value for prothrombin in the blood after the drug has been administered on two successive days. In our studies we have attempted to maintain the values for prothrombin in the blood between 10 per cent and 30 per cent, since our experiences have indicated that significant hemorrhage seldom occurs when the value for prothrombin in the blood is more than 10 per cent and that intravascular thrombosis seldom occurs when the value for prothrombin is less than 30 per cent. It is possible that dicumarol may be administered with satisfactory results if the value for prothrombin in the blood is not reduced as much as we have indicated.

The inexperienced may be confused by the use of the terms "prothrombin time" and "prothrombin percentage"; they do not have the same significance nor do they have a linear relationship. The laboratory should furnish to the clinician a chart by means of which he may convert prothrombin time into prothrombin percentage.[5] According to the technic used at the Mayo Clinic, a normal prothrombin time is 17 to 19 seconds; a prothrombin time of 27 seconds signifies 30 per cent prothrombin; 35 seconds signifies 20 per cent prothrombin and 58 seconds indicates 10 per cent prothrombin. However, in other institutions where different thromboplastins or technics are used in the performance of the prothrombin time test, quite different prothrombin times may correspond to values for 100 per cent, 30 per cent, 20 per cent and 10 per cent prothrombin.

Three hundred milligrams of dicumarol are given on the first day and 200 mg. on the second day. On each subsequent day when the prothrombin is more than 20 per cent, 200 mg. are given. On any day when the value for prothrombin is less than 20 per cent, dicumarol is withheld. There are minor variations of this program depending on sensitivity or resistance of a patient's prothrombin to dicumarol, which have been discussed in another publication.[2]

The Danger of Hemorrhage When Dicumarol Is Used

The sole danger associated with the use of dicumarol is hemorrhage. In our series of 1,983 postoperative cases minor hemorrhage (epistaxis, hematuria and localized ecchymosis) occurred in 3.4 per cent of cases and

* When both heparin and dicumarol are used, blood for determination of the values for prothrombin should be drawn not less than three hours after the last injection of heparin, since heparin itself modifies the result of the test for prothrombin.

serious bleeding (from operative wounds or from the gastrointestinal tract) occurred in 1.8 per cent of cases. One may expect minor bleeding in about one of each 25 postoperative cases and serious bleeding in about one of each 50 postoperative cases. There is a great difference between serious bleeding and fatal bleeding. Although marked bleeding from operative wounds occurred about 40 times during the course of treatment of almost 2,000 patients who had undergone operation, death from hemorrhage occurred only twice. Careful study of the records of these two fatalities, reported in detail elsewhere, indicates that the fatal hemorrhage could not definitely be attributed to the effect of dicumarol.[2] However, the two fatalities emphasize the ever-present danger of hemorrhage when dicumarol is used.

The Prevention and Control of Hemorrhage

The best method of preventing hemorrhage is to use dicumarol expertly. Even then, hemorrhage will occur. When epistaxis, hematuria and local ecchymosis are minor we do not ordinarily alter dosage but observe the patient for signs of more extensive bleeding. If bleeding from an operative wound is continued or marked, synthetic vitamin K (menadione bisulfite) should be administered intravenously in amounts of 60 mg. and transfusion of fresh blood should be used to restore the blood that has been lost. The injection of vitamin K can be repeated at two hour intervals, once or twice as needed.

Contraindications to the Use of Dicumarol

We use dicumarol cautiously or refrain from its use in renal insufficiency, which prolongs and enhances the effect of dicumarol, after operations on the brain or spinal cord, because bleeding in these regions might result in disaster, in blood dyscrasias with increased tendency to bleed because dicumarol will accentuate the tendency to bleed, in ulcerative lesions because of the tendency to bleed, and in nutritional deficiencies or hepatic diseases associated with potential or actual prothrombin deficiency. We doubt whether the use of anticoagulants adds anything to the treatment of subacute bacterial endocarditis and we do not use them in such cases, since the danger of hemorrhage is relatively great.

Experience in 2,019 Postoperative Cases *

The results of treatment in 352 cases of postoperative venous thrombosis are shown in table 1. In 832 cases of abdominal hysterectomy dicumarol was given prophylactically (table 2) because experience has indicated that in 4 per cent of such instances venous thrombosis occurs following operation; death from pulmonary embolism occurs in 0.7 per cent. In 329 cases of pulmonary embolism after operation anticoagulants were used (table 3). In

* In many instances of pulmonary embolism heparin and dicumarol were used. In most instances of venous thrombosis, dicumarol alone was used. In all instances in which an anticoagulant was used prophylactically, dicumarol only was used.

TABLE I

Results of Use of Anticoagulants in 352 Cases of Postoperative Venous Thrombosis

	Cases	
	Expected if Anticoagulants had not been Used*	Occurred
Subsequent venous thrombosis or pulmonary embolism	88	9†
Fatal pulmonary embolism	20	0

* On the basis of the rates given in the reports of Barker, Nygaard, Walters and Priestley.[6,7]
† In 3 cases the percentage of prothrombin in the blood was more than 30. In 1 case use of dicumarol had been discontinued and prothrombin was normal.

TABLE II

Results of Prophylactic Use of Dicumarol in 832 Cases of Abdominal Hysterectomy

	Cases	
	Expected if Anticoagulants had not been Used	Occurred
Venous thrombosis or pulmonary embolism	33	3*
Fatal pulmonary embolism	6	0

* Minor venous thrombosis.

TABLE III

Results of Anticoagulant Therapy in 329 Cases of Pulmonary Embolism

	Cases	
	Expected if Anticoagulants had not been Used	Occurred
Subsequent venous thrombosis or pulmonary embolism	144	3
Fatal pulmonary embolism	60	1*

* Occurred after prothrombin time had returned to normal.

addition to the cases considered in tables 1, 2 and 3, there were 470 instances in which dicumarol was used prophylactically to prevent pulmonary embolism and venous thrombosis. These were instances in which venous thrombosis or pulmonary embolism had occurred after previous operations or in which the prospects of postoperative venous thrombosis were considered relatively great. Venous thrombosis occurred in two instances. There was no instance of pulmonary embolism.

In 36 additional cases dicumarol was used prophylactically after amputation of a leg because of arteriosclerosis obliterans or thrombo-angiitis obliterans; there were no vascular complications except that bleeding into the region of amputation occurred in one instance. Unfortunately no figures

are available for comparison of results with and without anticoagulants. We can indicate only that dicumarol provided adequate protection against venous thrombosis in these cases.

An over-all consideration of the 1,513 cases presented in tables 1, 2 and 3 indicates that the following results were achieved: 85 patients survived who might have been expected to die had anticoagulants not been used; 250 patients were spared venous thrombosis or nonfatal pulmonary embolism. No great accuracy is claimed for these figures since alternate patients were not treated with and without anticoagulants; the control figures were calculated from experiences before anticoagulants were used. We recognize the deficiency in this method of study but the striking efficiency of anticoagulants in preventing pulmonary embolism and venous thrombosis is nonetheless impressive.

Additional Disadvantages of Anticoagulant Therapy

In considering venous thrombosis and pulmonary embolism there is one most desirable goal: absolute prevention. This has not been achieved. Table 2 illustrates the point well. Eight hundred thirty-two patients who had undergone abdominal hysterectomy were treated with dicumarol in order to save six lives and in order to prevent venous thrombosis and nonfatal pulmonary embolism in 30 instances. The returns might be considered small. The numerical results are more impressive in cases of venous thrombosis and nonfatal pulmonary embolism; yet it was necessary, in the aggregate, to treat 681 patients in order to save 79 lives and to prevent further venous thrombosis and embolism in 220 instances. We do not belittle these results. We only emphasize our inability to detect the predisposition to venous thrombosis *before it occurs.* Were it possible to designate the patients who would have venous thrombosis *before they had it,* treatment with anticoagulants would be even more productive. There has been a good deal of study on this phase of the problem of venous thrombosis and embolism; some progress has been made on the periphery but the hard core of the problem remains.

Comments on Ligation of Veins Versus Use of Anticoagulants

Our experience with ligation of veins has been very limited. That is a natural result of the gratifying experiences with anticoagulants that we have had. Furthermore, we do not know of any results from ligation of veins which approach in excellence those derived from our experience with anticoagulants. It is well to remember that the sole purpose of ligation of veins is to prevent pulmonary embolism. Also ligation of a vein will prevent pulmonary embolism only from that region which is distal to the ligature. Thus if the surgeon ligates the left superficial femoral vein he will prevent pulmonary embolism only from the left leg distal to the ligature. It is common experience that in such instances pulmonary embolism may originate from the right leg or from a region proximal to the ligature on the left.

Anticoagulants are used for two purposes: to prevent pulmonary emboli from originating anywhere in the body and to prevent extension of venous thrombosis. While it is more impressive to prevent pulmonary embolism, the importance of preventing occurrence or extension of venous thrombosis must be stressed. Any physician, observing the varices, edema, stasis dermatitis and cellulitis, and varicose ulcers years after a patient has had postoperative venous thrombosis, can testify to that. There is some difference of opinion in surgical circles as to whether or not ligation of veins contributes to the chronic venous insufficiency which might ordinarily result from venous thrombosis. Certainly ligation does not lessen venous insufficiency as anticoagulants do by preventing extension of the thrombosis.

Our carefully considered opinion, after weighing available evidence, is that the use of anticoagulants is, in general, a much better method of treatment than ligation of veins. We recognize a small rôle for ligation of veins, which is, at times, quite important, but we do not recognize superiority of this method in the type of case which has been considered in this presentation.

Anticoagulants in Acute Myocardial Infarction

Three previously published reports by others indicate the usefulness of anticoagulants in acute myocardial infarction.[8-10] Fifty patients who had this condition have been treated at the Mayo Clinic; the detailed report by Parker and one of us is available elsewhere.[11] One hundred cases observed at our clinic previously, before the use of anticoagulants, served as the control series.[12] In 10 of our cases heparin and dicumarol were used; in 40 cases dicumarol alone was used. There were no instances of peripheral arterial embolism or venous thrombosis. Pulmonary embolism which did not cause death occurred in one instance (2 per cent) at a time when the prothrombin in the blood was not satisfactorily reduced. Five patients died (10 per cent). Evidence of further myocardial infarction occurred in one instance (2 per cent). There was only one instance of serious bleeding, hemarthrosis of a knee joint. In the control group the incidence of pulmonary embolism, peripheral arterial embolism and venous thrombosis was 33 per cent, the incidence of further myocardial infarction was 15 per cent and the death rate was 13 per cent.

No final conclusion can be drawn from experience with 50 cases nor from the other individual reports. However, in the aggregate the results seem significant. Certainly there is no evidence of harm resulting from the use of anticoagulants in acute myocardial infarction. Final decision relative to the value of this type of treatment must wait on extensive experience with a large number of cases, such as that now being obtained by a coöperative study under the supervision of Dr. I. S. Wright and the American Heart Association.

We believe that both heparin and dicumarol should be used in the treatment of acute myocardial infarction, that treatment should be begun as soon

as possible after the diagnosis has been made and that it should be continued for at least four weeks.

Anticoagulants in the Postpartum State

Previous reports indicate that dicumarol may be used safely and with benefit in the treatment and prevention of venous thrombosis following delivery.[13, 14] Indeed the first dose may be administered prophylactically during labor and administration may be continued during the postpartum state without inducing uterine hemorrhage.[14] Dicumarol may appear in the milk of lactating animals to which it is given; indeed baby rats nursing from mothers receiving dicumarol may bleed and die.[15, 16] However, the dose (5 mg. daily) given to the mother rats produced prothrombin deficiency in their blood and caused them to die in six to nine days. The dose administered to the rats was many times greater than that given to patients, if body weight is considered. No conclusions can be drawn from these studies except that if rats are given excessive amounts of dicumarol, their milk may contain sufficient dicumarol to produce profound prothrombin deficiency in nursing young. There is no clinical corollary to this situation.

We have administered heparin and dicumarol or dicumarol alone to 19 postpartum patients, *four* of whom had pulmonary embolism and *15* of whom had venous thrombosis in the legs. Four of these patients had undergone cesarean section. Treatment was begun as early as the fifth postpartum day to patients who had vaginal delivery and as early as the eleventh day following cesarean section. There was no unusual bleeding although the values for prothrombin in the blood were mostly between 10 per cent and 30 per cent after the third day of treatment. In no instance was there further venous thrombosis or pulmonary embolism. Only two mothers were nursing their babies while they received dicumarol. Repeated studies of the blood of each baby indicated that the values for prothrombin were never reduced significantly; they were consistently between 90 per cent of normal and normal, even when the values for prothrombin in their mothers' blood were between 10 per cent and 30 per cent.

Our studies support the conclusions of previously published reports that anticoagulants may be used after delivery, as needed for the prevention and treatment of pulmonary embolism and venous thrombosis. The problem of prothrombin deficiency of babies induced by dicumarol in mothers' milk cannot be considered wholly settled, although prothrombin deficiency did not occur in our two cases. When dicumarol is given to a mother who is nursing a baby, it is probably the course of wisdom to give the baby vitamin K or to determine values for prothrombin in the baby's blood and to correct any deficiency of prothrombin which may occur.

Experience with Medical Patients

A group of 288 patients who had various kinds of vascular diseases have been given dicumarol as part of their program of medical treatment. A

summary of the diseases from which these patients were suffering and the results of anticoagulant treatment is given in table 4.

The three large groups consisting of those who had thrombophlebitis, pulmonary embolism or acute arterial occlusion are worthy of more detailed consideration.

TABLE IV

Results of Treatment of 288 Medical Patients with Dicumarol

Condition Treated with Dicumarol	Total Patients Treated	Subsequent Fatal Pulmonary Embolism	Subsequent Nonfatal Pulmonary Embolism	Subsequent Venous Thrombosis
Thrombophlebitis	138	0	2	4
Pulmonary embolism	44	0	1	0
Sudden arterial occlusion	45	0	0	0
Thrombo-angiitis obliterans	23	0	0	0
Arteriosclerosis obliterans	17	0	0	0
Miscellaneous*	21	0	0	0
Totals	288	0	3	4

* Includes patients who had chronic venous insufficiency, congestive heart failure, simple arterial thrombosis, cerebral thrombosis and other diseases.

Thrombophlebitis. In this group were 138 patients. The thrombophlebitis was of the idiopathic type (one episode) in 42 cases and of the recurrent idiopathic type (several episodes) in 27. In 16 cases the thrombophlebitis followed trauma, in eight it was associated with acute infections, in eight with carcinoma, in five with blood dyscrasias, in four with thromboangiitis obliterans and in 11 with miscellaneous conditions which may cause thrombophlebitis. In 17 cases the thrombophlebitis occurred in varices including incompetent greater and lesser saphenous systems.

In 90 cases the thrombophlebitis involved the iliofemoral or deep sural veins or both.

The chief reason for giving dicumarol was to prevent pulmonary embolism and further venous thrombosis. There is no reliable information available as to the incidence of subsequent pulmonary embolism or venous thrombosis among patients who have thrombophlebitis which does not follow operation but it is reasonable to assume that it may be about as high as in the group of patients who have iliofemoral or sural thrombophlebitis following operations.

In this group fatal pulmonary embolism did not occur; two patients had nonfatal pulmonary embolism during adequate prothrombin deficiency. In four cases subsequent venous thrombosis developed. In one of these cases it occurred after the administration of dicumarol had been discontinued because of difficulties in obtaining blood for prothrombin determinations and after the prothrombin value had returned to normal; in another the venous thrombosis occurred when the prothrombin value was greater than 30 per

cent. In the two remaining cases there was adequate prothrombin deficiency at the time of the development of the venous thrombosis.

Pulmonary Embolism. There were 44 patients in this group. The incidence of subsequent pulmonary embolism and venous thrombosis without anticoagulant therapy among medical patients who have iliofemoral or sural thrombophlebitis is unknown but it probably is the same as that noted among patients after operation.[6] In the group of medical patients with pulmonary embolism now being considered, who were treated with dicumarol, there was no subsequent fatal pulmonary embolism or venous thrombosis; one patient had another nonfatal pulmonary embolism when the prothrombin value was between 20 and 30 per cent.

Acute Arterial Occlusion. A more detailed report of our experience with the use of anticoagulants in the treatment of acute arterial occlusion has been given elsewhere. The results of the use of anticoagulants in the treatment of 15 of the 45 patients on whom we are reporting data were recorded in that report.[17]

We have treated, now, acute arterial embolism in 19 cases and acute arterial thrombosis in 26 cases with anticoagulants. The plan of treatment has included the use of dicumarol with a period of preliminary heparinization. The patients have been divided into two groups: those whose treatment was instituted early (within 24 hours) and those whose treatment could not be started until more than 24 hours had elapsed from the time of the occlusion. In the group of 11 cases of acute arterial embolism in which treatment was started early, there was survival of the extremity in 10 (91 per cent). In the group of eight cases in which treatment was late, the extremity survived in only two (25 per cent).

In the group of 16 cases of acute arterial thrombosis with early treatment, the extremity survived in 13 (81 per cent) whereas in 10 cases with late treatment the extremity survived in five (50 per cent). These data indicate that when anticoagulant therapy is used in conjunction with other methods of emergency treatment one may expect survival of the extremity in a large number of cases if the treatment is started soon after the occlusion has occurred.

Incidence of Bleeding in 288 Medical Cases. Two patients bled from the gastrointestinal tract and one had severe subcutaneous bleeding. Treatment was discontinued in all instances. All patients recovered. Minor bleeding (epistaxis, hematuria and petechiae) occurred twice. Treatment was continued in all instances. The incidence of bleeding (1.0 per cent for major bleeding and 0.66 per cent for minor bleeding) was markedly less than the incidence noted in the postoperative cases considered earlier in this presentation.

Duration of Administration of Dicumarol. The use of dicumarol in a group of patients with occlusive arterial disease who required treatment over a long period gave us the opportunity to observe the effect of prolonged administration of dicumarol in a small group. In 41 cases dicumarol was

given for as long as one month, in 25 for two months, in nine for three months, in three for six months and in one for 10 months. No conclusion could be reached relative to the effectiveness of anticoagulants in the chronic occlusive arterial diseases. No untoward effects which might have resulted from the prolonged administration of the drug were observed in any of the cases. The prothrombin activity returned to normal in all within a few days after the administration of the drug was discontinued.

Conclusions from Experience with Medical Patients

Our experiences indicate clearly that the anticoagulants are effective in the treatment and prevention of vascular thrombosis of medical patients just as they are effective in the care of postoperative patients with these conditions. Fatal pulmonary embolism can be prevented and venous and arterial thrombosis can be halted in most instances. Early treatment of sudden arterial occlusion with anticoagulants and other measures results in survival of the extremity in 90 per cent of instances of embolism and 80 per cent of instances of thrombosis.

Summary

1. The expert use of the anticoagulants, heparin and dicumarol, has improved tremendously the outlook for patients who have acute vascular thrombosis.

2. An over-all consideration of 1,513 postoperative patients treated with anticoagulants indicates that the following results were achieved: 85 patients survived who would have been expected to die from pulmonary embolism; 250 patients were spared venous thrombosis or nonfatal pulmonary embolism. In 506 additional postoperative cases in which dicumarol was used prophylactically, venous thrombosis occurred in but two instances; there was no pulmonary embolism.

3. A consideration of 288 medical patients indicates that fatal pulmonary embolism was prevented by anticoagulants. Nonfatal pulmonary embolism and venous thrombosis occurred very infrequently.

4. A study of 50 cases of acute myocardial infarction indicates substantial reduction in the incidence of further myocardial infarction and in arterial embolism and venous thrombosis.

5. Survival of the extremity occurred in 91 per cent of cases of arterial embolism and in 81 per cent of cases of arterial thrombosis, if treatment with anticoagulants was begun early and supplemented by other treatment.

6. In general, the use of anticoagulants constitutes the greatest contribution to the successful treatment and prevention of intravascular thrombosis and embolism.

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SOME OBSERVATIONS ON BLEEDING TENDENCY IN THROMBOCYTOPENIC PURPURA *

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In a previous communication it was reported that in irradiation hemorrhage (roentgen-ray) an anticoagulant was present in the blood.[1] This anticoagulant was indistinguishable from heparin. The hemorrhagic tendency in dogs could be prevented or stopped temporarily by the intravenous injection of protamine sulfate or toluidine blue. Both of these substances are capable of binding heparin and rendering it biologically inactive so far as its anticoagulant properties are concerned. They do not appear to affect any other phase of the clotting mechanism except to act as anticoagulants when present in excess.[1] These agents were effective even in the face of marked thrombocytopenia and did not alter the platelet count in these animals.

Total body irradiation is characterized by severe thrombocytopenia, a prolonged bleeding time and a prolonged clotting time. Aside from the prolonged clotting time, the hemorrhagic characteristics of this disease are similar to those of thrombocytopenic purpura in man, whether primary or secondary. The marrow picture in these disorders may vary from one of hyperplasia to complete aplasia, depending upon the marrow defect. Inasmuch as the thrombocytopenia, the prolonged bleeding time and the petechial hemorrhages appeared common to all of these disorders, it was decided to determine the heparin tolerance of normal and thrombocytopenic patients' bloods, and to establish what, if any, effect toluidine blue or protamine had upon the hemorrhagic tendency.

This report is primarily concerned with the results obtained from the intravenous administration of toluidine blue upon the hemorrhagic manifestations of thrombocytopenia. Attempts were made, however, to determine the effect of increasing amounts of heparin upon the whole blood clotting time of purpuric patients with thrombocytopenia. Similar control studies were made upon three to five normal bloods each time the thrombocytopenic patients were tested. In each case a series of 10 serology tubes were placed in a rack and to each was added small increasing amounts of protamine sulfate dissolved in normal saline. Blood was drawn from the antecubital vein into dry 10 c.c. syringes. This blood was then placed in a dry test tube. Eight c.c. were then rapidly pipetted into a second test tube

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containing 0.2 mg. of heparin (liquid). After gently mixing, 0.8 c.c. of blood was placed in each of 10 tubes, each of which contained increasing amounts of liquid protamine sulfate (0.00 mg. to 0.36 mg.). Micropipettes were used for both the heparin and protamine measurements, and in both cases the same stock solutions were used for the controls and the thrombocytopenic bloods. There was evidence that both the heparin and protamine solutions slowly deteriorated, but since these changes affected both the test and normal bloods, these changes did not appear to alter the clotting time relationships.

An example of the increased susceptibility of thrombocytopenic blood to heparin is demonstrated in figure 1. It will be noted that more protamine sulfate was necessary to restore the normal clotting time in the thrombocytopenic blood than was required by normal controls. This procedure was carried out daily for five days before toluidine blue was given. The clotting curves all followed similar patterns. The patient, suffering from idiopathic thrombocytopenic purpura whose blood had been thus tested, was then given dye (2.5 mg. per kg. of body weight). The following morning she was free from bleeding and no new petechiae had appeared. According to the patient she was free from oral bleeding for the first time in eight months. Twenty-four hours after the injection of toluidine blue her blood was again titrated for heparin tolerance. The results are also charted in figure 1. It will be noted that less protamine was necessary to restore normal clotting time than was required before the dye was injected. Not shown in this chart are data obtained the day following the second dye injection (1.5 mg. per kg. of body weight) when the heparin tolerance was entirely restored to normal.

A more extensive report upon this phase of the problem will be reported elsewhere.

Reported below is our clinical experience with toluidine blue administration as a means of aiding in the control of petechial hemorrhages in thrombocytopenia. This report is limited in experience and is comprised of six cases. Four of these were thrombocytopenic purpura associated with acute or subacute leukemia. Two were idiopathic thrombocytopenic purpuras. Two other cases were treated with favorable results but data were insufficient to justify inclusion here. The preliminary nature of this report is emphasized.

Case Reports

Case 1. L., a female, age 49, complained of malaise and increasing weakness of two months' duration. Three weeks before admission ecchymoses were first noted. Ten days later she was admitted to another hospital where a diagnosis of acute myelogenous leukemia was made. Her platelet count was 23,000 and the bleeding time was prolonged to more than an hour. She was given five transfusions during the next five days along with vitamin K, vitamin C, rutin and calcium gluconate. The bleeding persisted and became so marked that it was necessary for her to carry a basin constantly under her chin. There were, however, no oral ulcerations and the gums were not swollen when she was transferred to the Billings Memorial Hospital. The prothrombin time and whole blood clotting times were normal. The platelet

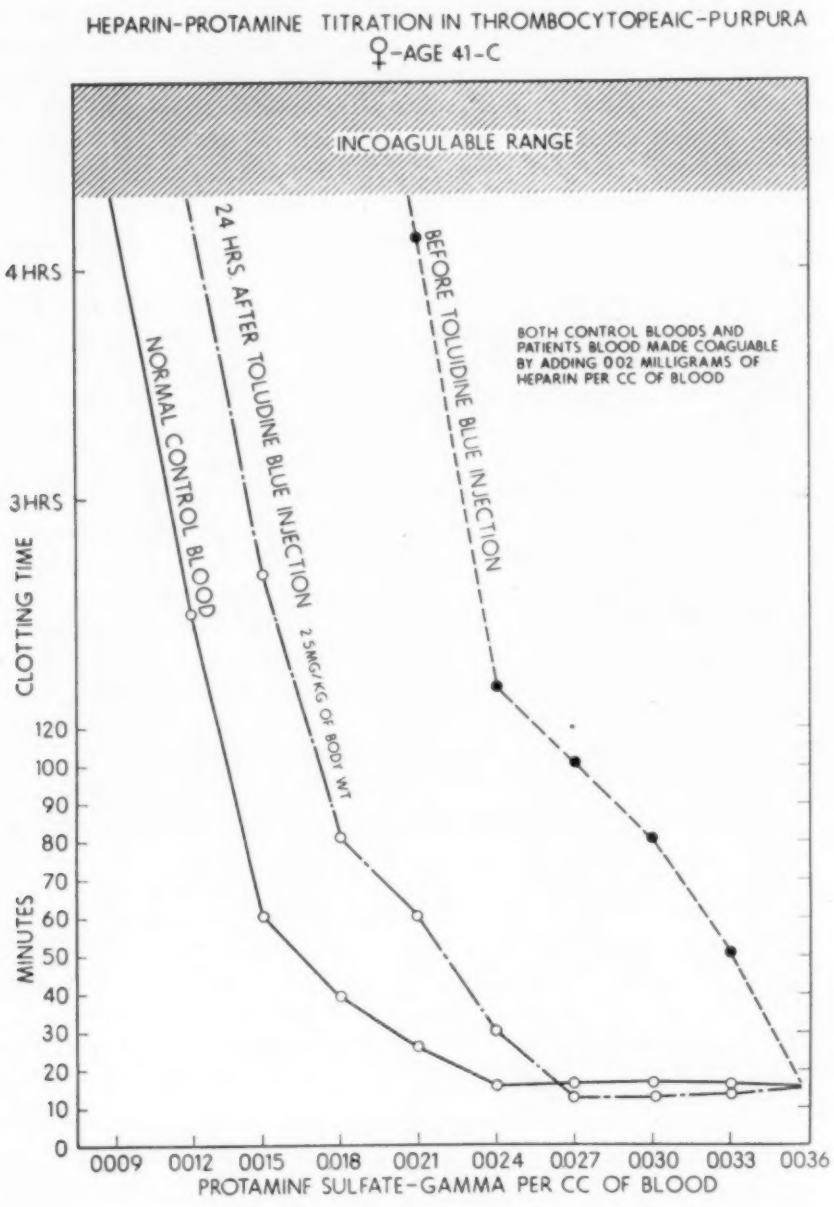
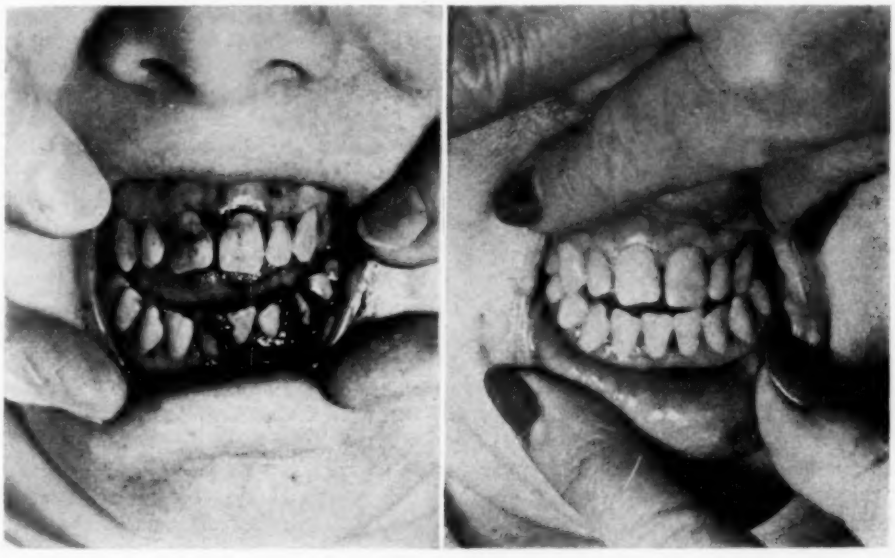


FIG. 1. In this chart is shown the amount of protamine sulfate required to restore the normal clotting time of whole blood made incoagulable by the in vitro addition of standard amounts of heparin. Twenty-four gamma of protamine were necessary to restore to normal the clotting time of normal blood, while 36 gamma were required to restore normal clotting time in the untreated thrombocytopenic patient (curve on far right). Twenty-four hours after toluidine blue injection the amount of protamine necessary to restore normal clotting time in this patient was 27 gamma per c.c. (see text).

count varied between 20,000 and 60,000 and the bleeding time was continually longer than one hour. The diagnosis of acute myelogenous leukemia was confirmed by sternal puncture from which she bled for two days. In view of the failure of other measures to control hemorrhage, she was given 2 mg. of toluidine blue in saline per kilo of body weight 12 hours after admission. The bleeding stopped within eight to 10 hours. A second dose of 1.5 mg. of dye per kg. of body weight was given the following day. The bleeding time was not shortened, but her petechiae began to resorb and no new ones appeared. Three days later oral bleeding again appeared at which time the original 2.0 mg. dose of dye was repeated. Bleeding stopped within 20 minutes but again the bleeding time was not shortened. Two days later oral bleeding again appeared. A photograph of her mouth at this time was taken (figure 2 a).



A B

FIG. 2. Two photographs of the mouth of a patient (Case 1) suffering from spontaneous oral bleeding from thrombocytopenia secondary to acute myelogenous leukemia. These pictures were made just before (*a*) and 12 hours after (*b*) the patient received toluidine blue intravenously. Observe the absence of oral ulcerations. Though the bleeding was controlled, the bleeding time was not shortened.

She vomited 400 c.c. of fresh blood. Three mg. of dye per kg. of body weight was given at this time and again all evidence of bleeding ceased within 20 to 30 minutes. The second photograph (figure 2 b) was taken 12 hours later. The patient was not allowed to wash her mouth for three hours before either photograph was made. Clinically the patient was improved and felt better when hemorrhage was absent. However, it did not affect the character of her primary disease, and she died seven days after her last dye injection.

Case 2. A 2½ year old female child was admitted from another hospital because of uncontrollable bleeding and tracheal compression from mediastinal and cervical nodes. A diagnosis of subacute leukemia was made five months before her admission to the Bobs Roberts Hospital. On admission to this hospital a diagnosis of monocytic leukemia was established. Enlarged lymph nodes, spleen and liver were observed. Oral ulcerations were present from which blood continued slowly to ooze. The platelet count ranged between 15,000 and 23,000. Because her condition ap-

peared terminal in spite of conservative measures and because her bleeding was not controlled by transfusions, vitamin K, or vitamin C, she was given 3 mg. of toluidine blue per kilo of body weight intravenously in 300 c.c. of normal saline. Seven of the nine subsequent days she received 2 mg. doses of the dye per kg. of body weight. Photographs of her mouth and forearms were taken before and after dye was injected (figure 3). The oozing about her mouth stopped after a few hours and no new petechiae appeared. The ulcerations about the gums began to heal. The clots formed scabs which were undermined with new epithelium. Subsequent photographs are shown which were taken during this process of repair. While the oozing abruptly stopped, nearly 10 days elapsed before the gums and lips were reëpithelialized. As in Case 1, the bleeding time was not shortened and the platelet count remained constantly below 50,000. This patient received some palliation but the ultimate course of her disease was not altered. She died two weeks after her last dye injection. The control of hemorrhage by the administration of dye, however, was striking. Within three days after the initial administration of the dye the petechiae had all disappeared (figure 4). Many ecchymotic areas continued to re-appear at the sites of needle puncture, but none appeared spontaneously or in the absence of trauma.

Case 3. An eight year old boy was admitted to the hospital with a diagnosis of subacute myelogenous leukemia of eight months' duration. He had received fresh whole blood transfusions on January 30, and February 2, 3, and 4, 1947. In spite of these measures, he developed gross hematuria and eye ground hemorrhages. Hence on February 5, 4 mg. of toluidine blue per kilo of body weight were administered by slow intravenous drip. Eight hours later the urine contained only 8 to 12 red cells per high power field. By the following day all evidence of bleeding had ceased. No new hemorrhages in the eye grounds appeared, and the old ones resorbed. The bleeding time continued prolonged and the platelet count remained below 50,000. Two days after the dye injection the child suffered a severe nasal hemorrhage at the site of an old intranasal ulceration which previously had bled. A freshly drawn 500 c.c. blood transfusion was given. The bleeding promptly stopped and the bleeding time dropped from 55 minutes to seven minutes.

In this case the tendency for spontaneous hemorrhage ceased after the administration of dye. As in Cases 1 and 2 the bleeding time was not shortened until a large fresh whole blood transfusion was given. Presumably the platelet count was sufficiently elevated to enable a normal platelet thrombus to form, thus shortening the bleeding time.

Case 4. A 45 year old male with subacute myelogenous leukemia known to be present for five months, became severely anemic and his platelet count fell to less than 50,000. Petechiae appeared over the lower extremities and oral bleeding occurred. Oral ulcerations were present and the gingival margins became edematous. The bleeding time exceeded 50 minutes on three occasions. He was given 2.0 mg. per kg. of body weight of toluidine blue; and 1.0 mg. per kg. the following day. No new petechial hemorrhages appeared and oral bleeding from the ulcerated areas was markedly reduced but not completely controlled. Twenty-four hours later a freshly drawn citrated whole blood transfusion was administered following which all evidence

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FIG. 3. This is a series of four photographs made over a 12 day period of the oral bleeding of a 2½ year old child suffering from subacute monocytic leukemia and secondary thrombocytopenia. Oral ulcerations were numerous about the lips as shown in photographs A and B. Toluidine blue was administered seven out of nine days (see text, Case 2). Photograph A was made immediately before the initial injection, photograph B was made two days later after two doses of dye had been given. Note that nearly all the gingival ooze had ceased but that the encrusted blood about the lips persisted although somewhat diminished. Photograph C was made on the ninth day after the patient received the last (seventh) dose of toluidine blue. On the fourteenth day, five days after the last dye injection, spontaneous bleeding again recurred as shown in photograph D.

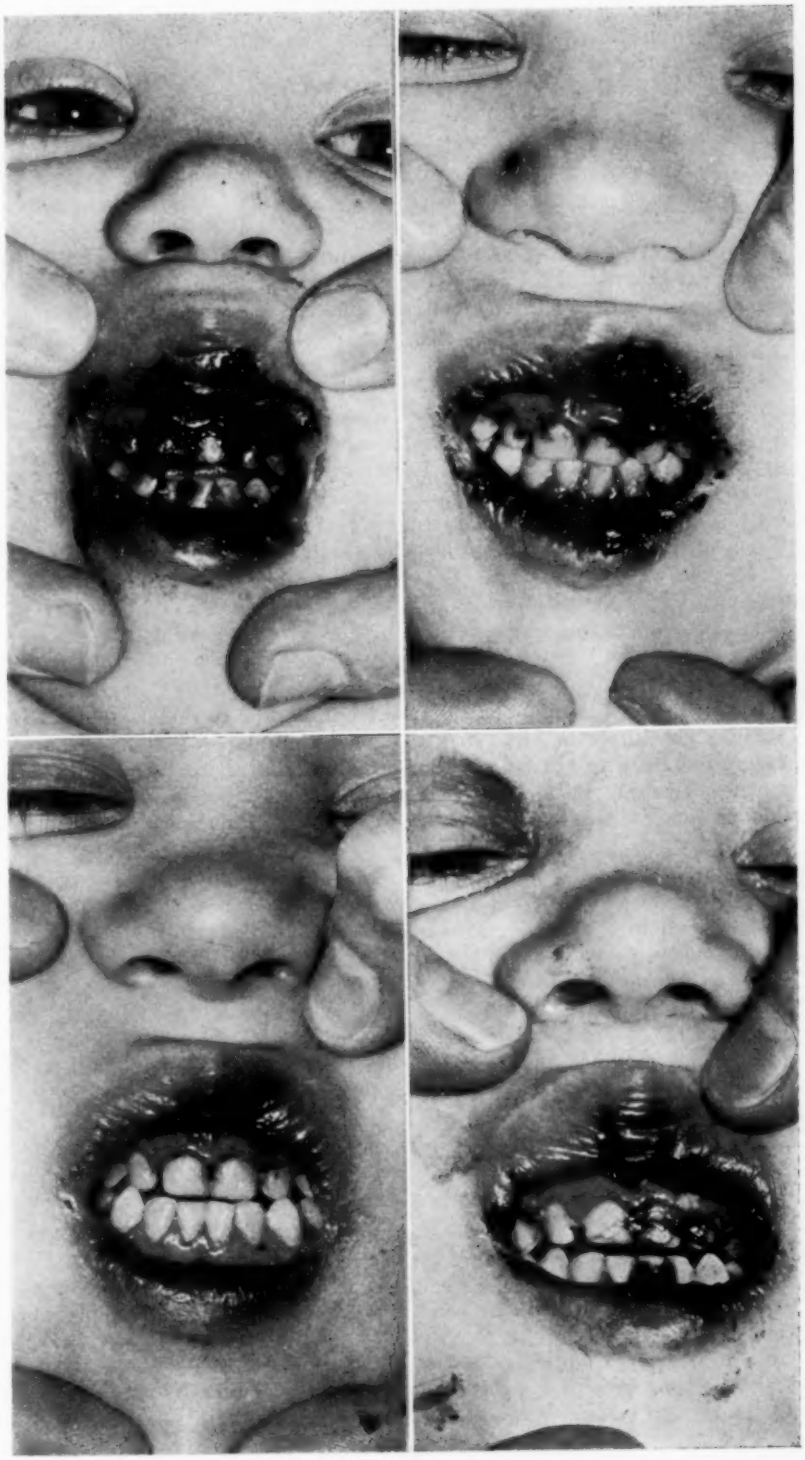


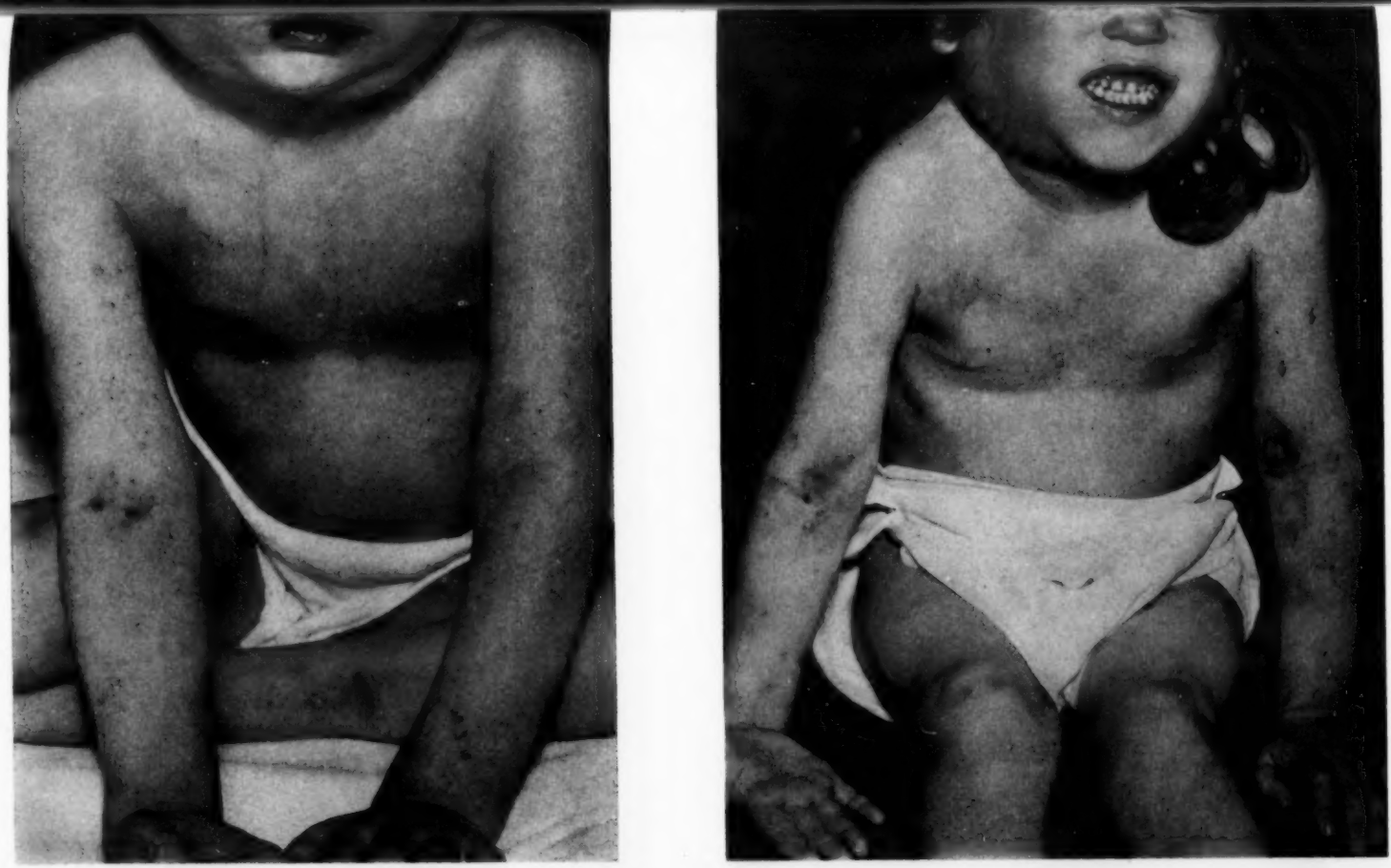
FIG. 3.

of bleeding promptly stopped. Transfusions given before dye injection had not altered the hemorrhagic tendency. As in Case 3, much of the bleeding appeared due to ulcerations which bled because the platelet count was low. Apparently the platelet thrombi were slowly formed and easily dislodged. This patient like Case 3 received maximum benefit when both blood and toluidine blue were given.

Case 5. A 22 year old female had a history of intermittent purpura of five years' duration. Splenectomy was performed when other methods failed to control bleeding. A prompt rise in the platelet count occurred. Six hours after splenectomy it was 420,000 per cu. mm. of blood. However, by the end of two weeks her platelet count was 140,000 and petechiae reappeared. At this time her bleeding time was 70 minutes. She was then given 2 mg. of toluidine blue in 500 c.c. of saline intravenously, and was kept ambulatory. No new petechiae appeared and the tourniquet test became negative. The bleeding time on this occasion was reduced to seven minutes. The platelet count continued to drop and reached 60,000 to 80,000 by the end of the third week even though splenectomy had been performed and all visible accessory splenic tissue had been removed. The bleeding time again became prolonged when the platelet count fell below 90,000, and at these low levels it was not shortened by the administration of the dye. New showers of petechial hemorrhages appeared when the dye was not administered. Transfusions, however, did not influence the formation of petechiae. Five weeks after splenectomy her menstrual period began. The flow was profuse and not relieved by transfusions or toluidine blue. However, she was not given the dye or blood together or on consecutive days. Hysterectomy was then performed and the patient made an uneventful recovery. Petechiae continued periodically and the thrombocytopenia and prolonged bleeding time were still present nine months after splenectomy.

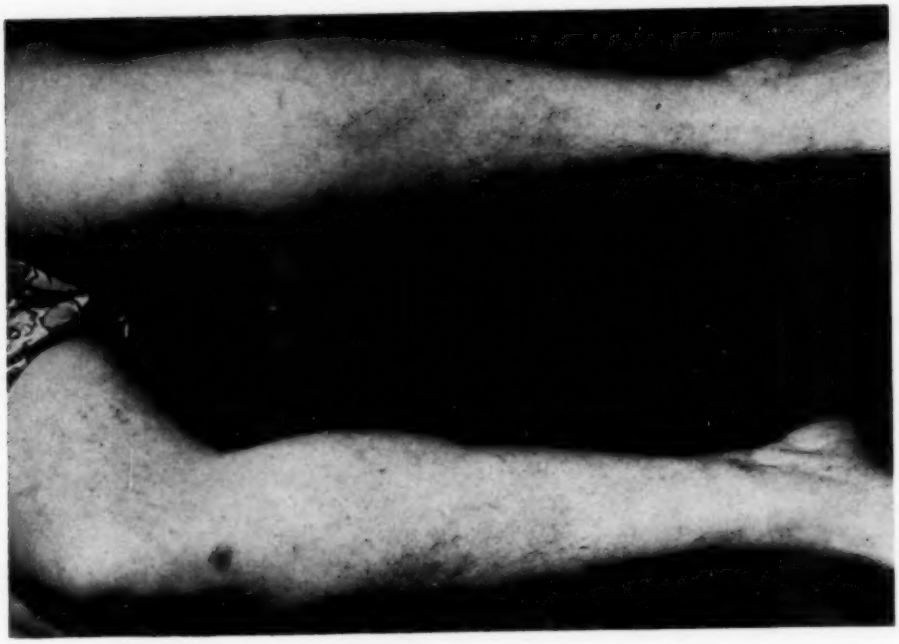
This patient is also of interest in that she was successfully delivered six months before splenectomy even though she suffered from marked thrombocytopenia (60,000) at that time. The infant at birth had a platelet count of 40,000 which, after three weeks, began to return to normal. It has remained normal for over one year. This finding argues strongly in favor of a circulating substance which is transmissible across the placental barrier and which then is capable of reducing the platelet numbers of the fetus.

Case 6 was a 41 year old female with idiopathic thrombocytopenic purpura who suffered from oral bleeding for eight months without remission. No drug or allergic history could be elicited. Repeated studies of the platelet count, bleeding and clotting times, sternal marrow studies, and the absence of other disease confirmed our diagnosis. Photographs of her lower extremities were taken before therapy was begun (figure 5 a). After a five day study period she was given toluidine blue (2.5 mg. per kg. of body weight). The following morning she was free from oral bleeding for the first time in eight months. No new petechiae could be seen, her platelet count remained at 60,000 and her bleeding time continued prolonged. On the third day photographs again were taken (figure 5 b) which showed some remission of her petechiae. The next day bleeding again occurred and new showers of petechiae appeared. The same dose of dye was again given with similar results. Four days later the dye was again given even though the patient was not bleeding. Splenectomy was refused and the patient was discharged. She was given toluidine blue in capsules to be taken orally. Each capsule contained 150 mg. of dye. The oral dye proved ineffective as it had in dogs.[1] She reported that she had taken one capsule daily but that on the fifth day heavy petechial showers appeared over the lower extremities and her oral bleeding returned. On this day she was seen in the Out Patient Department where 2.5 mg. of dye per kg. of body weight were given intravenously. Her bleeding stopped and no new petechiae appeared. She was readmitted to the hospital three days later and given two fresh whole blood transfusions daily for three days. After

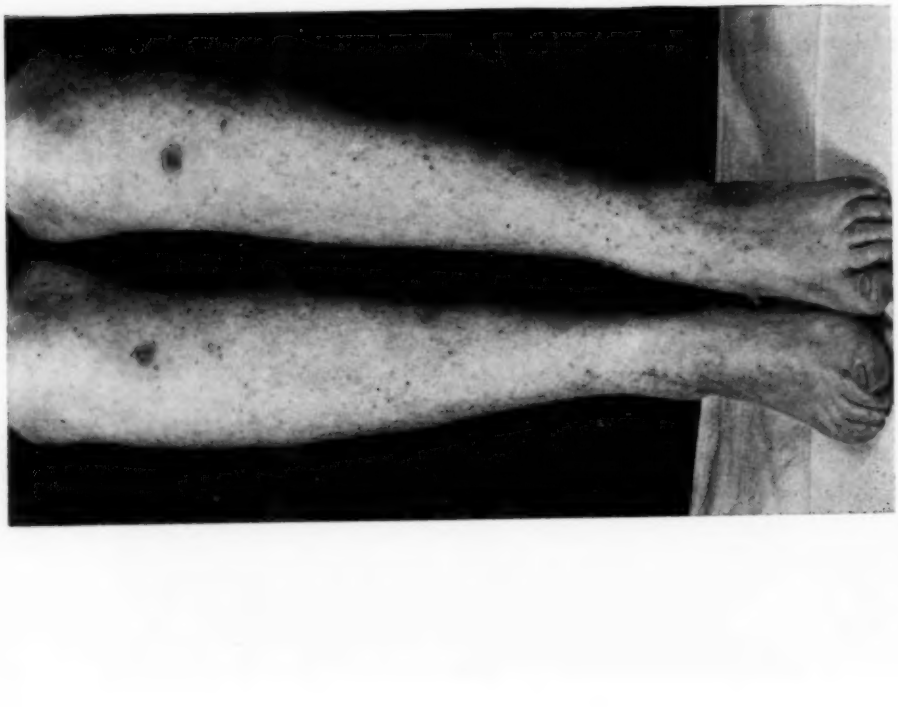


A B

FIG. 4. Photograph A shows many petechiae of the right forearm of Case 2 before dye injection. Photograph B, taken on the ninth day, shows no petechiae although many ecchymoses are present at the sites of vena punctures and penicillin injections. The bleeding time was not shortened.



B



A

FIG. 5. Photographs A and B of Case 6 were taken before (*a*) and three days after (*b*) a single injection of toluidine blue. A decrease in the number of petechiae is apparent. On the following day new showers of petechiae appeared but these were again controlled by the injection of the dye. The bleeding time was not shortened.

the second transfusion bleeding recurred and continued in spite of four more transfusions (500 c.c. each). The patient refused further therapy and died on the ninth hospital day from intracranial hemorrhage. Autopsy was not permitted.

Discussion

Thrombocytopenia is found in a number of blood disorders. Some of these disorders appear to be distinctly different and probably unrelated. For example severe thrombocytopenia may occur in pernicious anemia, aplastic anemia, and leukemia. Hemorrhage may appear in all three of these syndromes, but it is not regularly present in any one. Bleeding probably presents a greater problem in the acute leukemias than in aplastic anemia or pernicious anemia. In the latter it is apparently comparatively rare even though the thrombocytopenia may be severe.[2] These features do not argue for a similarity in the primary disease, but they do emphasize the need for a better knowledge of platelet physiology.

The importance of the platelet in the normal hemostatic mechanism is well established, although there has been some difference of opinion as to how they function in this respect. All are agreed that platelets rapidly agglutinate at the site of endothelial injury, and that the size of the platelet thrombus depends upon the number which flow past the traumatized area. In the smaller vessels (capillaries and venules) the platelet thrombus may be the only hemostatic mechanism necessary to control bleeding. In the larger vessels, fibrin formation plays the more important rôle and rapidly makes its appearance soon after the platelet thrombus begins to form.

The "sticky" or adhesive quality of platelets is well known. It is an important factor in causing the platelet to adhere and agglutinate at the site of vascular injury. Fibrin is deposited and becomes enmeshed in the plate thrombus which normally holds fibrin at the site of injury. When platelets are absent or reduced in number, the clots are friable and easily dislodged; hence in thrombocytopenia, clots form but they may be subsequently washed away and give rise to further hemorrhage.

Clot retraction or syneresis is greatly influenced by the platelet number. It may be absent or long delayed in thrombocytopenia. Syneresis is a function of the intact platelet as extracts of platelets are inactive in this respect.[3] As the clot retracts the rent in the vascular wall is partially or completely occluded and in this manner syneresis contributes to hemostasis.

Platelets are rich in cephalin and lipoproteins and are thromboplastic. A good portion of the platelet thrombus undergoes lysis, liberating thromboplastin. These thromboplastic substances are so generously contained in almost all body tissues that it seems unlikely that any diminution in platelet number should greatly alter the amount of thromboplastin available for clotting. The fact that the clotting time is normal in thrombocytopenia is evidence that an adequate amount of thromboplastin is available from other sources (erythrocyte, leukocyte, platelet, and surrounding tissue).

The platelet thrombus is the result of platelet agglutination, platelet adhesiveness and clot retraction. The platelet thrombus is probably indispensable to the normal mammalian hemostatic mechanism in vivo. Other factors may contribute to in vivo clotting but of those known, the formation of the normal platelet thrombus and the fibrin clot are most important. The platelet thrombus is the first observable response to vascular injury and in some cases it may be the only response. A deficiency in the platelet number retards the formation of the platelet thrombus and probably accounts for the prolonged bleeding time in thrombocytopenic purpura. The reduced platelet number impairs clot retraction and adhesiveness, resulting in friable, bulky and easily dislodged clots. These deficiencies probably account for the prolonged bleeding time in thrombocytopenia.

What can not be explained on the basis of thrombocytopenia is capillary fragility. It is possible that the platelets are normally concerned with the preservation of capillary integrity in some way not yet known. It has been suggested that they are normally concerned with "plugging" fenestra in capillary walls, although no evidence has been produced to show that such a phenomenon ever occurs. It is more likely that the increased capillary fragility is the result of other disturbances which accompany the appearance of thrombocytopenia. The disturbed capillary integrity in thrombocytopenic purpura may return to normal even though thrombocytopenia may persist, although usually these two phenomena coincide.[4]

The capillary factor is demonstrated by methods which either increased the intracapillary pressure (venous constriction) or by methods which lessen the extracapillary pressure (negative pressure). Because of the increased capillary permeability in thrombocytopenic purpura, the petechiae are gravitational in their distribution. The gravitational character of petechiae serves to emphasize the importance of the capillary defect and makes difficult an explanation of petechiae on the basis of thrombocytopenia alone.[5] In severe cases petechiae may appear even without gravitational influence although they are usually more numerous in the dependent portions of the body.

The importance of the capillary factor is demonstrated by the patient with thrombocytopenia but with remission of petechiae.[3, 4, 5] In such patients internal bleeding is not a serious problem, yet when spontaneous petechiae reappear the critical character of the disease is again apparent.

Successful treatment then must be directed at both the capillary defect and at restoring the platelet number. It is likely that a common agent is responsible for both defects and that its elimination would result in a cure of the disease. Thus far, no such factor has been identified, although in allergic purpuras relief from hemorrhage occurs as the allergic state subsides. Unless one concludes that the disease known as Werlhoff's disease is in reality an unidentified allergic state some other primary disturbance must be assumed. Until the primary disorder has been recognized, treatment must

be directed so as to correct both thrombocytopenia and the increased capillary permeability.

Some degree of palliation results from blood and plasma transfusions. The rise in platelet number is slight to moderate and may be enough to temporarily shorten the bleeding time (Case 5). There is some evidence that the plasma may contain some substance or group of substances capable of correcting petechiae in the less severe cases. However, it is because of the failure of this type of supportive measure that the use of splenectomy in the treatment of idiopathic thrombocytopenic purpura has persisted. Just why splenectomy should prove beneficial has never been clearly understood. The rise in the platelet number after splenectomy in Werlhoff's disease is often spectacular, but similar sharp rises in the platelet count (over one million) have been observed in patients where splenectomy is performed incidental to other surgical disease (carcinoma of the stomach).[6] It appears likely that the removal of the normal spleen in man permits thrombocytosis, and because of this fact splenectomy affords a convenient method of elevating the platelet count in idiopathic thrombocytopenic purpura. However, in secondary thrombocytopenia, splenectomy may be ineffective [5, 7] and its failure not understood.

In severe bleeding any measure that can aid in elevating the platelet count should be used. The hazards of impaired platelet thrombi formation and poor clot retraction have been discussed. Blood transfusions should always be used, especially in the postoperative patient with recurrence of thrombocytopenia and bleeding.

Our own limited experience with the use of antiheparin toluidine blue and back titrations of heparinized blood, suggests that in thrombocytopenia, an increased amount of heparin-like substance may be present in the blood. These patients appear to be improved; generalized oozing stops *except from ulcerated areas* when toluidine blue or protamine sulfate are given. The bleeding time is *not* shortened, but petechiae are held in check. If the ulcerated areas are allowed to crust over so that scales form, these may heal if the general tendency to ooze is controlled by frequent administration of blood transfusions and antiheparins.

The continued and joint administration of toluidine blue and blood to correct capillary defect and to restore the platelet thrombi formation to near normal appears to be more effective than either alone. The dye appears to be concerned more with the capillary disturbance than with the impaired platelet thrombi formation. The latter can only be corrected by the administration of fresh blood or plasma.

Toluidine blue or protamine are fairly well tolerated when given intravenously in man. We have administered the dye dissolved in 250 to 500 c.c. of normal saline. The dosage of each has ranged from 1 mg. to 4 mg. per kg. of body weight. The dye-saline or protamine-saline mixture were administered intravenously over a two hour period. An initial dose of about

2.5 mg. of either substance per kg. of body weight proved satisfactory. Each day thereafter 1.5 to 2.0 mg. was given until all oozing stopped and new petechiae no longer appeared. Usually 24 to 48 hours (or two to three doses) were sufficient. Thereafter 1.5 to 2.5 mg. per kg. dose was administered every second, third or fourth day or as bleeding recurred. Again, it cannot be overemphasized that while bleeding from oral or cutaneous ulcer may be lessened after dye or protamine administration, they usually will not entirely cease unless the platelet count is partially elevated by transfusions. When such bleeding persists after the appropriate administration of toluidine blue, fresh whole blood transfusions should be given.

Little is known of the toxicity of toluidine blue. In normal dogs we found it to be strongly hemolytic. Leukocytosis and thrombocytosis also occurred.[8] However, methylene blue, a closely related compound chemically, and known to be of low toxicity in man, was as toxic as toluidine blue when given intravenously to dogs at similar dosage levels. In man we have not seen this type of reaction within the dosage levels used. In fact, aside from apprehensiveness in two patients on one occasion each, no untoward effects were noted. Apparently the dye is excreted in the urine and into the intestinal tract as both the urine and the stool become highly colored. After a single dose of approximately 2.0 to 2.5 mg. per kg. of body weight the urine and stool remained colored for 36 to 48 hours. Most of the dye is excreted by the end of 24 hours, and in the doses that we used the patient's skin was not discolored. It remains to be seen whether patients receiving the dye shortly before death may not be discolored when embalmed as in the case when methylene blue has been given premortally.

Toluidine blue is not active when given orally to either dog or man within the range from 1 to 5.0 mg. per kg. of body weight. Its failure orally is probably due to absorption of dye by the mucoproteins of the intestinal tract. Protamine sulfate is not active when given orally either, presumably because of digestion within the intestinal tract.

Summary

1. The effect of toluidine blue administered intravenously on petechial hemorrhage in patients with thrombocytopenic purpura is described.

2. Preliminary evidence is presented which suggests that the blood of thrombocytopenic patients tolerates heparin less well than does normal blood.

3. The dye appears to affect capillary permeability, aiding only in controlling petechiae. The bleeding time is not shortened and bleeding from ulcerated or denuded areas is not materially altered, unless whole blood transfusions are given or spontaneous platelet elevation occurs.

4. These observations are probably of greater physiologic interest than therapeutic value in these diseases.

5. The preliminary nature of these observations is emphasized.

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THE VALUE OF SPINAL FLUID EXAMINATION AS A DIAGNOSTIC PROCEDURE IN WEIL'S DISEASE*

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IT is well known that inflammation of the meninges may occur in Weil's disease, and that meningitis may occasionally be the principal clinical manifestation of that infection.[1, 2, 3] More commonly, however, meningeal involvement is evidenced only by abnormal changes in the spinal fluid. In cases observed recently at Grady Hospital, examination of the spinal fluid has revealed positive findings in Weil's disease with sufficient frequency to indicate that the procedure is of value as a diagnostic measure. This is important, in view of the fact that there is no satisfactory test for Weil's disease which is generally available or which gives a result quickly. The purpose of the present communication is to report the spinal fluid findings in our cases, together with similar information collected from the medical literature.

INCIDENCE OF ABNORMAL SPINAL FLUID FINDINGS

The present series is comprised of 14 cases in adults, observed during the years 1943 to 1946. All had typical manifestations, including jaundice. The diagnoses were verified by agglutination test, muscle biopsy, or both. In six cases there were signs or symptoms suggesting the possibility of meningitis, such as nuchal rigidity, severe headache or convulsive seizures. The spinal fluid findings in this group of cases are listed in table 1. We have classified cell counts higher than 5 per cu. mm. as abnormal. It will be observed that in 13 of the 14 cases abnormal spinal fluid findings were noted at one or more examinations.

In a survey of the literature on Weil's disease, from 1916 until the present, comparable data were obtained on 83 cases. We did not include single case reports, or reports which did not give information regarding both positive and negative spinal fluid findings. The groups were unselected, except that patients with syphilis were excluded. As shown in table 2, spinal fluid abnormalities were found in 65, or 83 per cent, of 78 cases. When added to our 14 cases the total incidence is 78, or 86 per cent, of 92 cases. Clinical signs of meningitis were present in 41 per cent of cases in the combined series.

TYPE OF SPINAL FLUID ABNORMALITY FOUND

Table 3 summarizes the spinal fluid abnormalities in a series of 97 patients, composed of the cases in table 2, together with five isolated case re-

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TABLE I

Details of Spinal Fluid Findings in 14 Cases of Weil's Disease

Pt.	Day of Disease	Meningeal Signs	Jaundice	Pressure (mm. sp. fl.)	Color	WBC's	Polys Per Cent	Lymphs Per Cent	Pandy	Protein (mg./100 c.c.)	Mastic
WKC	7th	+	+	110	0	5	50	50	Neg.	34	000000
	10th	0	0	—	0	0	—	—	—	—	—
HR	10th	+	+	Normal	Yellow	85	12	88	+	—	000000
MW	6th	0	+	Increased	Yellow	18	50	50	Tr.	54	111110
JV	12th	0	+	—	Yellow	27	37	63	+	75	000000
EH	14th	0	+	110	Yellow	17	0	100	Neg.	46	000000
DC	7th	0	+	—	0	46	40	60	+	28	000000
WBD	10th	0	+	130	Yellow	58	0	100	++	90	110000
	21st	0	0	140	0	9	0	100	Neg.	27	—
	37th	0	0	100	0	2	0	100	Neg.	27	000000
WP	11th	+	+	150	Yellow	65	0	100	Tr.	72	000000
CC	7th	0	+	—	Yellow	210	1	99	Neg.	74	000000
	14th	0	+	—	Yellow	95	1	99	Tr.	73	000000
JP	9th	0	+	146	Yellow	167	0	100	+	300	111100
	21st	0	+	170	0	5	20	80	+	45	—
JT	7th	+	+	170	Yellow	55	50	50	Neg.	72	000000
	17th	0	0	—	0	2	0	100	Neg.	—	—
NY	6th	+	+	340	Yellow	36	44	56	Neg.	49	000000
AC	5th	0	+	120	Yellow	38	0	100	Neg.	48	000000
	7th	0	+	—	Yellow	740	30	70	Neg.	—	—
	23rd	0	+	—	Yellow	0	—	—	Neg.	—	—
JES	8th	+	+	300	Yellow	147	41	59	—	134	—

TABLE II

Incidence of Abnormal Spinal Fluid in Patients with Weil's Disease

Cases Reported by:	No. of Cases	No. with Abnormal Spinal Fluid	Per Cent with Abnormal Spinal Fluid	No. with Signs of Meningitis	Per Cent with Signs of Meningitis
Walch-Sorgdrager[3]	19	15	79	12	63
Costa and Troisier[4]	18	15	83	18	100
Clapper and Myers[2]	10	9	90	3	30
Ashe, et al.[1]	5	4	80	2	40
Minkenhof[5]	8	7	88	0 (?)	0
Cochez and Fichet[6]	3	2	67	3	100
Goldberg and Davens[7]	2	2	100	1	50
Garnier and Reilly[8]	11	11	100	3	27
Bruno, Wilen and Snavely[9]	2	0	0	0	0
Cargill and Beeson	14	13	93	6	43
Total	92	78	86	38	41

ports from the literature.[10, 11, 12, 13, 14] The commonest positive finding was an increase in the number of cells. There was considerable variability in total count, the range being 6 to 3000 cells per cu. mm., although in most instances it did not exceed 100 per cu. mm. The peak of the elevation occurs between the fifth and ninth days of illness.

TABLE III

Incidence of Individual Spinal Fluid Abnormalities

Abnormality	No. of Examinations	No. Abnormal	Per Cent Abnormal
Xanthochromia	29*	27	90
Increased cell count	97	84	87
Increased pressure	43	22	51
Positive Pandy	44	26	59
Increased protein	52	26	50
Positive mastic	18	4	22
Low sugar	35	1	3

* Only jaundiced patients are included in this group.

TABLE IV

Day	Cell Count		Differential	
	No. of Cases	Average Cell Count	No. of Cases	Average Per Cent Lymphocytes
4th	3	11	2	68
5th	6	145	4	65
6th	11	128	10	61
7th	16	585	13	50
8th	8	383	6	30
9th	4	207	4	75
10th	7	74	7	85
11th	4	42	4	86
12th	2	215	1	41
13th	3	166	3	100
14th	3	65	3	93
15th	2	55	2	60
16th	1	6	0	—
19th	2	19	2	96
21st	3	9	3	93
22nd	1	9	1	100

The data on differential cell counts are summarized in table 4, where it will be seen that lymphocytes usually predominate, although during the first week of disease as many as 50 per cent of the cells may be polymorphonuclear leukocytes.

Xanthochromia was the only other positive spinal fluid finding which occurred with sufficient frequency to be of significance as a diagnostic aid. As shown in table 3, this was noted in 90 per cent of cases with jaundice; it was never found in patients without jaundice. The color varied in intensity from a faint yellow to a deep gold. This coloring is presumed to be due to bilirubin, which gains entrance to the spinal fluid in Weil's disease

as a result of the inflammatory changes in the meninges. In other diseases associated with icterus the spinal fluid does not become discolored unless the jaundice is severe and of long duration. We have recently observed two illustrative cases: one, a patient with Weil's disease, had xanthochromia at a time when his serum icterus index was only 27; the other, an infant with congenital atresia of the bile duct, had colorless spinal fluid at a time when the serum icterus index was 150. It appears, therefore, that xanthochromic spinal fluid in a patient with mild jaundice is a point in favor of the diagnosis of Weil's disease.

The Diagnosis of Weil's Disease

Any simple procedure which will assist in the early diagnosis of Weil's disease is of value. None of the usual diagnostic measures is entirely satisfactory. The demonstration of leptospirae in the blood is only possible during the first few days of illness, and in unskilled hands false positive reports are liable to occur. Guinea pig inoculation with blood or urine will only be positive if done at certain stages of the disease, and the procedure requires time and experience. The agglutination test is reliable, but a good antigen—preferably live leptospirae—must be available, and antibodies may not be demonstrable until late in the course of the infection. Biopsy of striated muscle reveals characteristic lesions in many instances,[15] and has, in our experience, been of considerable help in the diagnosis of Weil's disease.

Summary

Of 14 cases of Weil's disease observed during a four year period, 13 were found to have abnormal spinal fluid. In only six of these cases were there clinical signs which could be attributed to meningeal irritation.

A search of the literature revealed 78 comparable cases in which spinal fluid findings were given. In 65 of these abnormal spinal fluid had been found. Combined with the series of cases reported in this article the incidence of abnormal spinal fluid in 92 cases of Weil's disease was 78 (86 per cent).

The commonest abnormality was an increase in the cell count. Xanthochromia was noted in approximately 90 per cent of the cases in which jaundice was present.

Spinal fluid examination is of value as a routine diagnostic procedure when the diagnosis of Weil's disease is suspected.

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PRESSOR ACTIVITY OF DESOXYCORTICOSTERONE ACETATE IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS *

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Previous studies [1] have demonstrated that the administration of desoxycorticosterone acetate (DCA) and sodium chloride to patients without hypertension or adrenal disease may be associated with an increase in blood pressure. Significant changes were not apparent until the second or third week of drug injection.

Because of the possibility that the adrenal cortex might be concerned in the development or maintenance of hypertensive vascular disease in man,[2, 3] the blood pressure response of hypertensive individuals to DCA was compared to that observed in subjects without hypertension.

Methods

Observations were made on 10 normotensive subjects and 14 patients with uncomplicated hypertensive vascular disease on the wards of the Presbyterian Hospital and the Research Service, First Division, of the Goldwater Memorial Hospital. Age and sex distribution were similar in both groups. All patients were afebrile, free of albuminuria or renal complications. The hypertensive subjects had no history, signs, or symptoms of cardiac insufficiency, and the venous pressure was normal in all instances.

Blood pressures were measured each morning in the same arm by the same observer, with the subject in bed with a 30 elevation of the upper body. More than five readings (and usually seven or eight) were taken and the lowest systolic and diastolic values recorded. Preliminary observations were carried out for at least two weeks, followed by a final base line period of one week during which systolic and diastolic readings fluctuated within a range of 10 mm. of mercury or less.

All subjects were weighed before breakfast on the same scales. The daily fluid intake and urine output were recorded. Patients were given a constant diet and fluid intake, with the total dietary and added sodium chloride varying between 5 and 10 gm. a day but maintained constant for each subject by means of weighed salt shakers. DCA † was injected sub-

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cutaneously for one week in doses of 5 mg. twice daily. In five subjects of each group fasting blood samples for hematocrit, chloride, sodium and potassium determinations were obtained before and after one week of DCA administration and the serum volume measured with the blue dye T. 1824.

Results

The effect of DCA on normotensive and hypertensive subjects is shown in figure 1. The administration of this steroid for one week failed to alter the "resting" blood pressure significantly in the 10 members of the control group. In contrast, definite elevation of systolic and diastolic readings took place in one to four days in the 14 hypertensive individuals, the mean systolic rise reaching a maximum of 24 mm. of mercury on the sixth day, the mean diastolic rise 15 mm. of mercury.

The expected changes in weight and hemodilution which follow DCA administration were noted in both groups, together with slight reduction in urinary volume and evidence of chloride retention.[4] No consistent alteration in serum chloride or sodium values was observed, but reductions in serum potassium levels from 0.1 to 0.8 milliequivalents per liter were found in both series. The serum volume increased in the normotensive subjects and in four of the five hypertensive patients studied; the largest rise was in some of the controls in whom no significant blood pressure increase was noted. Electrocardiograms and teleroentgenograms taken before and after one week of DCA administration in three members of each group revealed no changes. In one of the hypertensive subjects in whom a marked rise in blood pressure followed DCA, ballistocardiographic tracings in the control period were unchanged after one week of drug injection.

Comment

The rise in "resting" blood pressure observed within a few days after the sustained administration of DCA in hypertensive subjects cannot be ascribed alone to excessive retention of salt or water in the circulating blood. The weight, serum volume, hematocrit, urine volume and chloride changes were not more marked than those seen in normotensive individuals, in whom no significant pressor response was elicited during one week of DCA administration. The absence of alterations in the ballistocardiogram of one hypertensive patient points against a significant change in cardiac output in this subject.

Although the prolonged administration of DCA may give rise to a gradual increase in blood pressure in patients without hypertension or adrenal disease, it would appear that an accelerated response to DCA may be found in hypertensive vascular disease. Evidence is lacking as to whether the more immediate rise in blood pressure is a sequel to the hypertensive state, or is in some way related to its cause. Studies are in progress to determine the rôle of sodium chloride in this accelerated pressor response.

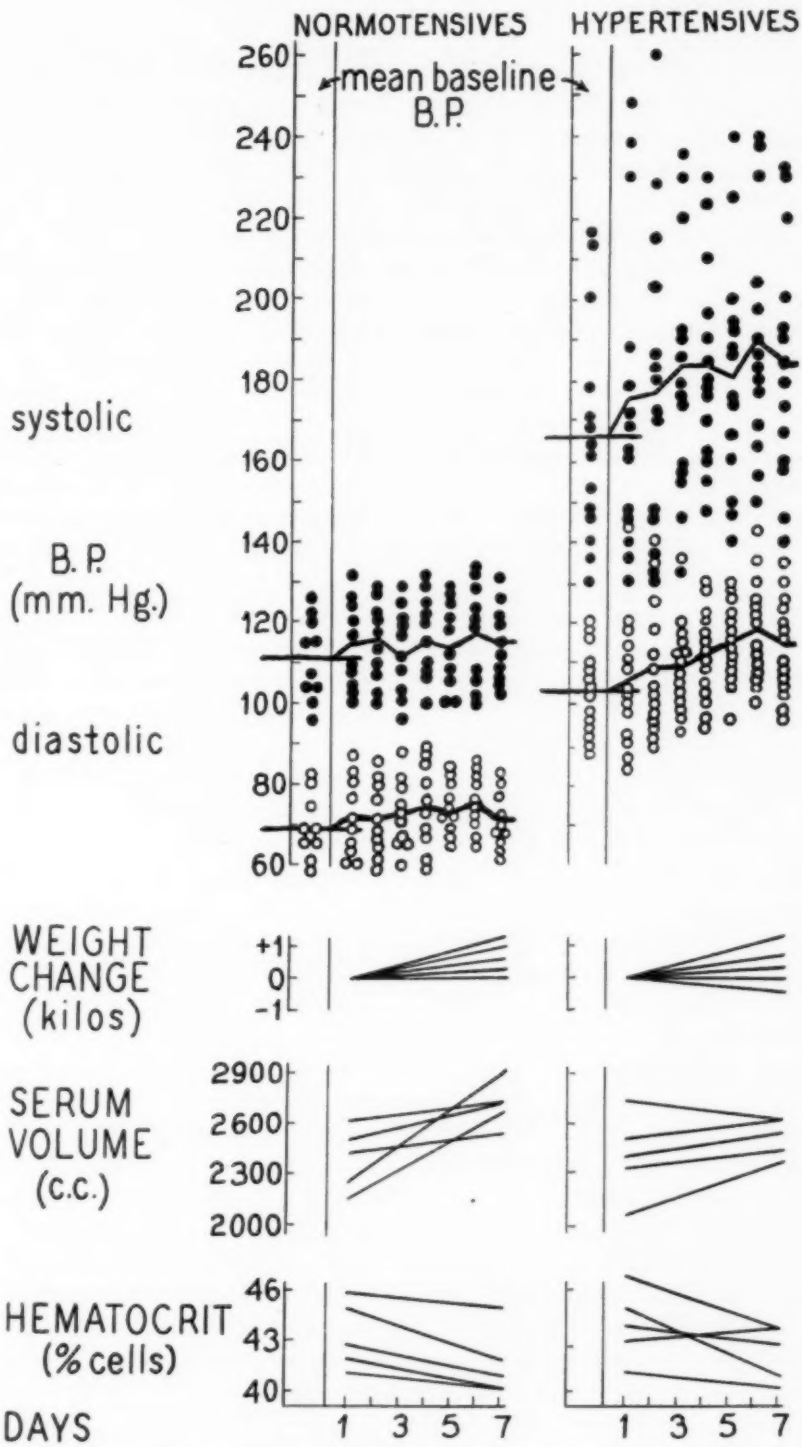

FIG. 1. Effect of DCA on normotensive and hypertensive subjects.

Conclusions

1. Desoxycorticosterone acetate was administered to 10 normotensive subjects and 14 patients with uncomplicated hypertensive vascular disease in doses of 5 mg. subcutaneously twice daily for one week.

2. No significant change in "resting" blood pressure appeared in the normotensive group, whereas definite increases in systolic and diastolic readings were observed in the hypertensive patients.

3. The prompt rise in blood pressure of patients with hypertension could not be ascribed to changes in salt or water retention alone as there were comparable changes in the normotensive group.

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DISSECTING ANEURYSM OF THE AORTA:

A REVIEW OF 17 AUTOPSIED CASES OF ACUTE DISSECTING ANEURYSM OF THE AORTA ENCOUNTERED AT THE MASSACHUSETTS GENERAL HOSPITAL FROM 1937 TO 1946 INCLUSIVE, EIGHT OF WHICH WERE CORRECTLY DIAGNOSED ANTE MORTEM *

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IN 1937 Glendy, Castleman, and White [1] presented a clinical and anatomical analysis of 19 cases of dissecting aneurysm of the aorta which had come to autopsy at the Massachusetts General Hospital over the period of 1897 to 1936, inclusive. In 13 of this number the dissection could be described as acute or directly related to the death of the patient, while in six it was discovered incidentally, the patient having died of other causes. In only two of the 13 acute cases had a correct antemortem diagnosis of dissecting aneurysm been established, and yet the authors felt that the clinical picture had been sufficiently dramatic in most instances to warrant consideration of such a process. Also, in order that this consideration, together with such diagnostic procedures as might be attempted on a seriously ill patient, should allow a correct clinical diagnosis to be made in a greater percentage, if not in the majority, of such cases, they particularly emphasized (1) the type of pain most likely to be encountered and its manner of onset and radiation (especially to the back), (2) the likelihood of collapse with a blood pressure maintained at hypertensive level, and (3) evidence of arterial obstruction due to involvement of aortic branches in the dissecting process.

In order to evaluate the results of the interest thus stimulated in the recognition of this condition clinically, we have made a comparative study in this hospital covering the subsequent 10 year period from 1937 to 1946, inclusive. For the sake of easy reference and comparison, we shall adhere in general to the plan of presentation adopted in the earlier article. No attempt shall be made to enter into a historical review of the subject nor to augment further the numerous attempts at detailed pathological classifications and descriptions of the underlying medial disease. For a comprehensive and dependable presentation of these topics, the reader is referred to Shennan,[2] Glendy, Castleman, and White,[1] Sailer,[3] and, for the most recent complete review, Leitch.[4] In the following discussion we shall adhere to the term "dissecting aneurysm of the aorta," as it is at present generally accepted in both its clinical and pathological aspects.

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The present report includes only those cases of dissecting aneurysm in which there had occurred a spontaneous rupture of the intima with either extensive medial dissection or unquestionable medial disease. During the 10 year period 1937 to 1946 seventeen such cases were encountered among 3,876 necropsies (0.44 per cent) at the Massachusetts General Hospital. All of these evidenced fresh dissection within the coats of the aorta, and in three there were found old, healed, dissected aneurysms as well. In seven of the 17 cases an antemortem diagnosis of dissecting aneurysm of the aorta had been established, and in an additional case (Case 5), who experienced two acute episodes of dissection, the diagnosis was correctly made during the first episode. In two of our cases in which the diagnosis was established only at necropsy there was a history of clinical syphilis with syphilitic heart disease, positive serology, and extensive antisyphilitic therapy. At necropsy these were the only two cases showing a limited aortic dissection based on medial disease and in addition presenting the typical findings of syphilitic aortitis.

TABLE I

Seventeen Cases of Dissecting Aneurysm of the Aorta Coming to Autopsy at the Massachusetts General Hospital (1937 to 1946 inclusive)

Case No.	Sex	Age	Occupation	Necropsy No.	Year
1*	M	58	Clerk	8646	1937
2	F	78	?	8776	1938
3[5]**	M	69	Executive	9189	1939
4[6]	M	59	Chauffeur	9299	1939
5[7]	M	49	Plumber	9360	1939
6	F	71	Housewife	9388	1939
7[8]	M	58	Promoter	9791	1940
8[9]	F	57	Housewife	9997	1941
9[10]	M	49	Laborer	10023	1941
10[11]	F	60	Housewife	10235	1941
11[12]	M	52	Attorney	10322	1942
12[13]	M	69	Physician	10460	1942
13[14]	M	47	Merchant	10552	1942
14[15]	M	49	Laborer	10964	1943
15[16]	F	66	Housewife	11192	1944
16[17]	M	59	Retired	11258	1944
17[18]	M	50	Laborer	11850	1945

* Negro.

** The reference number indicates that this case has been previously published in "Case Records of the Massachusetts General Hospital."

Abstracted details of case histories and postmortem findings have been omitted for the sake of brevity. However, an individual chronological listing of the cases is presented (table 1), and the more important clinical and autopsy findings have been subsequently tabulated. Fourteen of these cases have already been published as individual case reports in "Case Records of the Massachusetts General Hospital" and are included in our references.[5-18]

Incidence, Sex, Age, and Occupation

Glendy, Castleman, and White [1] reported the postmortem incidence of the acute type of dissecting aneurysm of the aorta, as one in 635 (table 2). In reviewing their figures on frequency of occurrence, it may be ascertained that for the fourth 10 year period, 1927–1936, the incidence was one in 376 for the acute type. In the present series of cases, all acute, there occurred one in 228 autopsies. No adequate explanation for this apparent increase in incidence has been forthcoming, and indeed it may be of little significance when compared with other reported series which also vary widely. Weiss [19] in 1935 reported a postmortem incidence of dissecting aneurysm of one in

Table II

Postmortem Incidence of Dissecting Aneurysm of the Aorta at the Massachusetts General Hospital

Period	Necropsies	Cases Dissect. Aneurysm	Incidence
1937–1946	3876	17	1:228
1927–1936	3009	8	1:376
1897–1936	8255	13	1:635

300; McGeachy and Paullin [20] in 1937 of one in 500; Flaxman [21] in 1942 of one in 714; Sailer [3] in 1942 of one in 464; Logue [22] in 1943 of one in 143, and Leitch [4] in 1944 of one in 261. These figures could be misleading in that they may have been computed by different methods of analysis, and it may be said that the comparisons made in the table referred to here were based on comparable series in the same hospital.

The sex incidence in acute dissecting aneurysm is reported by various authors as ranging from two to one, to three to one, with the male sex predominating. This ratio is well maintained in the present series, in spite of the limited number of cases considered, there being 12 males and five females (table 3). It is interesting to note, however, that when the sex distribution

Table III

Sex and Age Incidence

Sex	No. Cases	Age Extremes	Average Age
Male	12	47–69	55
Female	5	57–78	66
Total	17		59

is compared to that of age, females tend to dominate the upper age brackets. As shown, the age extremes among the males were 47 and 69 years, with an average of 55 years, while those of the females were 57 and 78, with an average of 66 years. This determines an overall age average of 59 years, which is in accord with other observations and is in nowise distorted by in-

clusion of the unusual cases encountered at extreme age levels. It is of further interest to realize that the sex-age relationship portrayed here resembles that found in other degenerative vascular conditions attended with vascular accidents.

Occupation and race appeared to be of little significance, with only four of this group falling in the laboring class and only one being a negro.

Data as to Patient's History and Factors Related to Onset

A history of cardiovascular disease could be established in every case of this series. Arterial hypertension of either permanent or temporary character had been observed before the onset of aortic dissections in every instance. Congestive heart failure had occurred in four instances, angina pectoris was described in three others, and three of the patients had received antisyphilitic treatment. One of the latter, however (Case 1, negro, male), in whom systolic and diastolic aortic murmurs were present, had a consistently negative serological reaction and at autopsy showed no evidence of syphilitic infection. In the other two the presence of syphilitic disease was unequivocal. Such an incidence of syphilis complicated by dissecting aneurysm must be considered unusual.

A great deal of emphasis has been placed by some authors [2, 23] on the relationship of the acute onset of symptoms due to aortic dissection to physical exertion or emotional stress. An understanding of the process renders this a logical likelihood. However, in only two of the cases studied in the present analysis could the onset be clearly related to exertion; emotional disturbance seemed to play no part in any. In two there was a suggestive relationship between the onset and the eating of a meal.

Symptoms and Signs

The sudden onset of symptoms is generally considered characteristic of acute dissecting aneurysm of the aorta. Such an onset occurred in 14 of our 17 cases, and only in one could no history suggestive of the time of onset be obtained, while in two others gradually developing substernal pain was the initial warning. Pain was the initial symptom in 13 of the 16 cases of recognized onset, one was seized with sudden severe dyspnea, and in two syncope initiated the attack. In the remaining case, which presented congestive heart failure, it was not possible to find any symptom suggestive of the acute dissection found at necropsy.

At the onset or during the course of the acute episode, pain became the outstanding symptom in 15 of the 17 cases (table 4). In the majority of these it was persistent and often uncontrollable. Pain of dominating character was described as being substernal in four instances; in the back, usually in the interscapular region, in three; diffusely in the anterior part of the chest in six; and as being localized in the abdomen in two. Referred pain

was described in the back in five instances, in the arms in four, in the head and neck in three, in the legs in five, and in the abdomen once. It is to be recognized that the so-called referred pain was sometimes due to actual involvement of particular aortic branches in the dissecting process; especially did this seem to be true when the great vessels of the arch or the iliac arteries

TABLE IV

Location, Occurrence, and Radiation of Pain

Location	Initial Occurrence	Radiation
Chest—substernal	4	
anterior (diffuse)	6	2
back	3	5
Legs		5
Arms		4
Head and neck		3
Abdomen	2	1
No pain	2	
Total	17	

were involved. However, as will be considered later, pain of an altogether similar character often occurred when no such involvement of the corresponding vessels was demonstrable at autopsy.

Since pain is the leading symptom on which to base a clinical suspicion of the nature of the underlying process, a correlation of the manner of its onset and severity becomes as important in reaching a correct diagnosis as its location and spread. As may be seen (table 5), 10 of the 15 cases developed

TABLE V

Manner of Onset and Severity of Pain

	No. of Cases
Manner of onset of pain:	
sudden (8 severe; shock in 4)	10
gradual (none severe; shock in 1)	5
no pain (shock in 1)	2
Total	17
Severity of pain:	
severe (all sudden; shock in 4)	8
moderate (2 sudden; shock in 1)	7
no pain (shock in 1)	2
Total	17

pain suddenly, and in eight of these pain was classed as severe. In every case in which the pain was classed as severe the onset was sudden. Four of the six cases who developed symptoms of severe shock fell into this sudden-severe pain group. In all five of the patients in whom pain developed gradually it was classed as moderate or subject to control, while of the seven who evidenced moderate pain only two had a sudden onset. Shock occurred in only one of those with gradual onset of pain in the moderately severe group. Rather unusual, it seems, for such a small series is the fact that two of the 17 patients complained of no pain at any time during the course of their ill-

ness. One of these (Case 11) evidenced shock and survived 48 hours after onset. The other (Case 6) was in congestive heart failure and possibly died at the moment of onset.

At some time during the course of the acute illness there developed other symptoms of prominence which could be considered compatible with, but not characteristic of, dissecting aneurysm. Severe shock occurred in six cases, in two of which the onset had been initiated by syncope. Dyspnea became an outstanding symptom in six cases but did not persist in the one who had evidenced it at onset. Aggravating nausea and vomiting occurred in three instances, and deep cyanosis developed in two.

Blood Pressure

Considering a blood pressure above 140 mm. of mercury systolic and 90 mm. diastolic as abnormal, a history of hypertension was established in every case of this series. Case 10, which showed no cardiac enlargement clinically, by roentgen-ray or at necropsy had been observed in transient bouts of hypertension (table 6).

Table VI

Blood Pressure Levels Before and After Onset of Final Episode

Blood Pressure	History	Observed Before	Observed After
Above 140 mm. systolic and 90 mm. diastolic	17	9	10
Below 140 mm. systolic and 90 mm. diastolic	0	0	4 (shock)
Not recorded	0	8	3
Total	17	17	17

Blood pressure readings were recorded in nine cases shortly before the onset of the final episode and in 14 after the onset. Of the latter number, the four individuals in whom the blood pressure was within normal limits or low, evidenced a state of shock. In the cases in whom the blood pressure was dependably recorded both before and after dissection there appeared to be a consistent drop in pressure, which, however, tended to remain at hypertensive levels. In one case only (Case 4) the blood pressure recorded after the accident was higher than before. It seems to us rather unusual that the diastolic pressure tended to fall out of proportion to the systolic pressure initially, with a consequent increase in pulse pressure, but the preëxisting wide pulse pressure mentioned as being a factor in producing intimal rupture could not be substantiated in this group. That the persistence of hypertensive levels in this condition may be considered as a differential point against coronary occlusion seems to be the general opinion, but no comparative studies of hypertensive patients incurring coronary accidents have been found. However, Chambers [24] in studying 100 cases of acute myocardial infarction, con-

firmed by positive electrocardiographic findings, states that hypertensive patients suffering this accident showed a consistent drop in blood pressure, which, however, tended to remain at hypertensive levels. It would seem, therefore, that the initial level of blood pressure might determine in the absence of shock the levels observed after onset in both these conditions and that the apparent discrepancy is based on the fact that the incidence of hypertension is much greater in dissecting aneurysm and the survival period far shorter.

Heart Size

To facilitate comparison of heart size as determined clinically, by roentgen-ray, and at autopsy, these observations have been tabulated in table 7.

Table VII

Observations on Heart Size

Method	Normal Size	Enlarged	No. of Cases
Clinical	2	13	15
Radiographic	3	5	8
Anatomic (weight)	1	16	17

In the 15 cases on which such observations were recorded, the heart was reported as being enlarged on physical examination in 13 and normal in two. Of the eight cases examined radiologically, five were reported as showing cardiac enlargement and three normal heart size. At autopsy 16 of the 17 cases studied showed a definite increase in heart weight well above normal, associated with left ventricular hypertrophy. In the one instance (Case 10) which did not show any cardiac abnormality, the heart had been recorded as of normal size both clinically and by roentgen-ray. It will be remembered that this patient gave a history of only transitory hypertension.

Heart Murmurs

Auscultatory findings were described in 16 of the cases presented. Murmurs were heard over the basal area in nine of these patients, a diastolic murmur alone in two, and both systolic and diastolic in seven (table 8). In one of the last-mentioned, systolic and diastolic murmurs were heard also at the apex. In four cases (1, 6, 9, 14), including the two with syphilis, the diastolic murmur at the base had been heard prior to the onset of aortic dissection. In five cases (5, 7, 8, 13, 17) it was recorded as having been heard after the onset, but in only two of these (Cases 5 and 17) was it definitely determined to have been absent previously.

An attempt to correlate the incidence of aortic diastolic murmurs with the accident of dissection on such data would be misleading; yet one cannot escape the fact that the ratio is much higher than might be expected among average hypertensive patients.

Evidence of minimal disease of the aortic leaflets was determined at autopsy in eight instances, six of which were of a sclerotic and two of an inflammatory nature. There was no correlation to be drawn between these changes in the aortic leaflets and the existence of the basal diastolic murmurs, as in six of the cases presenting murmurs the leaflets were described as being normal.

TABLE VIII

Incidence and Types of Cardiac Murmurs in 16 Cases

Murmur	Apical	Basal	No. of Cases
Systolic alone	3	0	3
Diastolic alone	0	2	2
Systolic and diastolic	1	7	8
None			3

In view of the foregoing, we believe that the presence of a diastolic murmur at the base may take on an added significance when the clinical picture warrants suspicion of aortic dissection.

OTHER PHYSICAL FINDINGS

Other physical findings to which may be attributed particular significance in this condition are those associated with the involvement of the aortic branches in the dissecting process. This is especially true in involvement of the carotid arteries giving rise to cerebral manifestations and of the iliacs suggesting embolism. When the latter occurs initially, it is not unusual for operative relief to be attempted, as happened in one of these cases (Case 8). Such signs when added to a clinical picture otherwise suggesting aortic dissection may easily become pathognomonic. However, their occurrence is not sufficiently common (five in 17 cases) to warrant awaiting their development to venture a positive diagnosis.

TEMPERATURE, PULSE, AND RESPIRATION

In this series of cases there occurred no extreme variations in temperature, pulse, or respiration. In the absence of shock, a moderate increase above normal in all three was the usual finding. The maximum temperature recorded was 102° F., and the highest pulse rate 120. The heart rhythm was uniformly regular.

LABORATORY FINDINGS

The white cell count recorded in five of our cases ranged from 10,000 to 15,500, with a moderate increase in polymorphonuclear cells. Blood counts had not been done sufficiently frequently to indicate any significant drop in red cells, even though such might have occurred. The Hinton serological

reaction was determined in five cases and found to be positive in two of the three which had previously been diagnosed as having syphilitic infection. In five of the six patients on whom urine analyses were done there occurred abnormal amounts, alone or in combination, of albumin, and of red blood cells, white blood cells, and casts in the sediment. There seemed to be no consistent correlation between these findings and the involvement of the renal arteries by the dissecting process, but red blood cells in the urine following a period of anuria in one of the cases was probably due to involvement of a renal artery.

The electrocardiogram was recorded at least once in 14 of the 17 cases. There was slight to marked left axis deviation in 12 of these and a definite pattern of "left ventricular strain" in seven. There were additional changes in four which suggested the presence of coronary heart disease. The tracings in no case could be considered entirely normal and yet changes definitely suggestive of an acute myocardial infarction were never present. This was consistently true even in those cases in which the coronary arteries themselves were involved in the dissection.

The incidence of cardiac enlargement by roentgen-ray study has already been considered. Tortuosity of the aorta was described in seven of the eight cases examined, and in four of these dilatation was also present. In three instances in which successive roentgenological examinations were made changes in size or contour of the aorta were discovered, and in one of these it was reported as being compatible with dissection of the aorta.

Clinical Diagnosis

Seven of the 17 cases came to autopsy with a diagnosis of dissecting aneurysm of the aorta (table 9). The diagnosis was made at one time in another case which merits a special note. This patient (Case 5) survived

Table IX

Clinical Diagnosis

Dissecting aneurysm	8*
Acute coronary occlusion	4*
Rupture of a non-dissecting thoracic aneurysm	3
Malignant hypertension with hypertensive encephalopathy	1
Embolism	1
Congestive heart failure	1
Total	18*

* One case with two separate episodes of aortic dissection was correctly diagnosed once and mistaken for acute coronary occlusion the second time.

17 months after his first dissection, which was rightly diagnosed, but the second dissection, which occurred five and a half days before death, was thought to be an acute coronary occlusion. (This case appears under both diagnoses in table 9.) A final diagnosis of coronary occlusion, which condition is most frequently confused with dissecting aneurysm, was made in

four instances. Three cases were diagnosed as having rupture of a thoracic aneurysm, two of which were thought to be due to syphilitic involvement and the third to an arteriosclerotic process. Malignant hypertension with hypertensive encephalopathy was considered as the primary cause of death in one, embolism in the leg in another, and congestive heart failure in the remaining case.

Survival

The estimated period of survival is based on the length of life following the onset of the terminal episode. A special reference is added for the three cases which survived by three months, 17 months, and four and one-half years their initial dissection (table 10). Nine died within the first 24 hours

Table X

Period of Survival After Onset

Survival Period	Acute Dissecting Aneurysm	Old Dissecting Aneurysm
24 hours and less	9	
1 day to 6 days	6	
3 months	?	1
17 months	(5.5 days)	1
4.5 years	(sudden death)	1
unknown	2	
Total cases	17	
Average	43 hours	

and six within one to six days, with an average survival of 43 hours after the onset of the terminal episode. In their paper Glendy, Castleman, and White [1] reported a survival period for the acute cases of 4.15 days. This survival period is twice as long as ours, and we are unable to explain the discrepancy. The actual survival time in two instances could not be established (Cases 6 and 14). Of the three with healed dissecting aneurysms, one survived the initial episode by 17 months (Case 5) and another by 4.5 years (Case 16). The last case mentioned presented a second healed dissected aneurysm which had no doubt occurred three months before his last accident. In the third case, which survived the first episode by three months, the survival time of his terminal attack could not be determined.

Anatomical Cause of Death

The underlying cause of death was considered by the pathologist to be acute dissection of the aorta in every case, but in only two of the 17 could it be considered the immediate cause of death. In the other 15 death was no doubt primarily due to hemorrhage into serous or tissue spaces, with or without demonstrable rupture of the adventitia (table 11). The most frequent, as usually described, was hemorrhage into the pericardial sac with cardiac tamponade which occurred in 14 of our 17 cases. In three of this number the hemorrhage into the pericardium was associated with hemorrhage into

the left pleural space, in two into the mediastinum, and in two into the peritoneal cavity. In only one instance was there hemorrhage into other areas, namely, mediastinum and left pleural space, in which the pericardial sac was not involved. Thus, in this series, it can be stated that rupture into the pericardium with resulting cardiac tamponade was by far the most frequent immediate cause of death, which is in accord with the stated conclusion of many others. The remaining two cases, as noted above, died without external hemorrhage from the aortic wall.

TABLE XI

Location of External Hemorrhages

Pericardium	14
Pleural spaces	4
Mediastinum	2
Peritoneum	2

LOCATION OF INITIAL AND SECONDARY TEARS

Tears in the aortic intima, classified as initial, were located in the upper aorta in 19 instances, 16 of which presented evidence of recent occurrence, the other three having appeared to be well healed and communicating with dissected endothelialized aneurysmal sacs (table 11). Eleven of the 19 initial intimal tears were located within the first three centimeters of the ascending aorta, six in the ascending aorta beyond the 3 cm. level, one in the arch, and the remaining one in the thoracic aorta.

TABLE XII

Location of Initial and Secondary Tears in the Aortic Wall

Location	Intimal	Adventitial	Rerupture into Arterial Lumen
In first 3 cm. of ascending aorta	11 (2 old)	13	
In ascending aorta beyond 3 cm.	6	0	
In aortic arch	1	0	
In descending thoracic aorta	1 (old)	2	
In abdominal aorta			2
In iliac arteries			4
Total	19	15	6

It was more difficult to identify the site of the rupture of the adventitia through which blood escaped from the sac into the surrounding tissues or serous cavities. Sometimes it seemed that there had occurred a separation of the fibers of the outer coat, permitting diffuse penetration of blood, rather than a definite rupture of the coat. Of the 15 instances in which rupture of the adventitia with hemorrhage could be localized, 13 had occurred within the first 3 cm. of the ascending aorta, and the majority of these at the approximate level of the accompanying intimal tear. In two instances the

rupture had occurred in the thoracic portion of the aorta. In two instances the hemorrhage had extended along the adventitia of the pulmonary arteries, even reaching the lung parenchyma.

Rerupture of the dissecting aneurysmal sac into the original lumen was discovered in six instances, in two of which the secondary tear had occurred in the abdominal portion of the aorta and in the other four in one of the iliac arteries. Two of the cases (Cases 5 and 16) showing rerupture into an arterial lumen, both by way of the iliac arteries, had survived the initial episode by 17 months and four and a half years respectively. The other healed dissecting aneurysm (Case 14) apparently had been quite limited during the initial episode, the exact time of which is thought to have been three months before the final illness. It was believed that the terminal episode in this case was due to a marked extension through the original tear without rerupture into the aorta having ever occurred. The other four cases (4, 11, 12, 13) showing rerupture into an arterial lumen during their terminal episode survived the onset by 12, 24, 48, and 96 hours respectively. The idea that rerupture of dissecting aneurysm into an arterial lumen increases the chances of survival is no doubt based on the fact that most cases in which complete healing occurs show a free secondary communication between the sac and the lumen. That so many patients succumb in the initial attack in spite of such a communication would indicate that its occurrence is not the overall determining factor in length of survival after onset.

Extent of Aortic Dissection and Involvement of Other Blood Vessels

For the purpose of classification only the length of the aortic dissection is considered. It is recognized that the extent of dissection around the aorta is just as important from the standpoint of correlation with aortic branch involvement, but its variability renders description difficult except where it is

Table XIII

Extent of Aortic Dissection and Involvement of Other Blood Vessels

Length of Dissection	No. Cases	Coronary	Vessels of Arch	Celiac Axis	Renal	Mesenteric	Iliac
Limited	2	1					
Moderate	3		1				
Extensive	12	2	5	5	6	5	8
Total	17	3	6	5	6	5	8
Incidence of related symptoms		2	6	1	1?	2	6

complete or almost so. Thus we have considered the extent of dissection as limited when it involved only the ascending aorta, as moderate when it included the arch as well, and as extensive when it involved the aorta beyond the arch (table 13). In only the two cases (9 and 14) in which syphilitic

aortitis was present had the dissecting process been limited to the ascending aorta. That localized fibrosis of the media due to the syphilitic process tends to limit dissection along this otherwise diseased coat has been mentioned several times.[1, 2, 25] Dissection described as moderate had occurred in three instances, and in the other 12 the dissection had extended to or beyond the bifurcation of the abdominal aorta.

Considering involvement of the main branches of the aorta in the dissecting process in order of frequency, the iliac arteries were affected in eight cases, the great vessels of the arch in six, the renal arteries in six, the celiac axis in five, the mesenteric arteries in five, and the coronary arteries in three. That symptoms suggesting extension of the dissecting process into these arteries are not always evident has already been mentioned. A correlation between instances of actual vessel involvement and symptoms presumably consequent thereto is shown in table 13. Symptoms suggesting the possibility of such vessel involvement with no comparable lesion demonstrable at autopsy occurred in the legs in one case, head and neck in two, and abdomen in two.

An arteriosclerotic involvement of some part of the aorta was described in every case. Medionecrosis, which is now recognized as being by far the main etiologic factor of dissection of the aorta, was found in 13 cases; it was not typical in two cases and was absent in the other two cases.

Discussion

The increasing frequency with which a correct antemortem diagnosis is being made in dissecting aneurysm of the aorta within the past decade seems to be well brought out in this report. There is no doubt that this is primarily due to the widespread interest created in this condition by the work of Shennan.[2] He was able to report only a 2 per cent correct antemortem diagnosis in his review of 300 cases (1934). This interest was given an added impetus in this hospital through the efforts of Glendy, Castleman, and White,[1] who reported a correct antemortem diagnosis in 15 per cent of their small series (1937). Leitch [4] collected 282 cases, which included all those having occurred after Shennan's report to the time of his publication (1945). In 56, or 20 per cent, of these cases a correct antemortem diagnosis had been made. In the present series the condition had been clinically established in 41 per cent and suspected in another case in whom, during a previous accident, the diagnosis was rightly made.

The extension of pain from its initial location, which is usually in the thorax, to the head and neck, back, abdomen, or lower limbs, while often of an almost pathognomonic value, should not be considered necessary to make the diagnosis of dissecting aneurysm. In the light of our findings it would appear that associated pain in the arms should not be given too much emphasis in differentiating dissecting aneurysm from acute coronary occlusion without other evidence, particularly electrocardiographic.

Conclusions

1. A clinical and anatomical analysis of 17 cases of acute dissecting aneurysm of the aorta occurring at the Massachusetts General Hospital over the past 10 years (1937 to 1946) is presented.

2. A correct antemortem diagnosis was made in eight instances, in one of which a second and fatal attack was wrongly interpreted.

3. The manner of onset and the severity and spread of pain are the most reliable symptoms on which to base a diagnosis of dissecting aneurysm.

4. A history of hypertension has been established in every individual of this series. Evidence of hypertensive heart disease was found in all but three cases, two of which showed syphilitic heart disease.

5. Basal heart murmurs, particularly diastolic, were encountered sufficiently often to warrant consideration of their diagnostic significance.

6. The absence of characteristic electrocardiographic changes suggesting myocardial infarction should be given much weight in reaching the diagnosis of dissecting aneurysm in equivocal situations.

7. In spite of the fact that a definite diagnosis is not always easily reached, even when the condition is suspected, there has been a marked increase in the antemortem recognition of dissecting aneurysm during the past decade.

We wish to express our appreciation to Dr. Benjamin Castleman for his painstaking analyses of this condition in the cases presented and for his helpful criticism of the manuscript.

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THE USE OF FOLIC ACID IN THE TREATMENT OF ANEMIA OF RHEUMATOID ARTHRITIS—A PRELIMINARY REPORT *

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Introduction

It is well established on sound evidence that rheumatoid arthritis is a systemic disease.[1, 2, 3, 4] The most dramatic manifestation is usually a polyarthritis. However, associated fever, anorexia, weight loss, muscle atrophy, iritis, elevated sedimentation rate, and anemia, and the often dramatic relief with jaundice,[5, 6] or pregnancy,[7] prove conclusively its generalized nature.

Of all the associated symptoms of rheumatoid arthritis almost consistently present is a hypochromic microcytic anemia of an appreciable degree.[8, 9, 10] Of 50 cases of rheumatoid arthritis chosen at random from our files the average initial hemoglobin before treatment was 11.04 grams, the average erythrocyte count was 4,550,000, and the color indices averaged 0.82. Of these 50 patients those with the more severe form of the disease had a corresponding anemia of a more profound degree with hemoglobins of below 9.0 grams, erythrocyte counts of normal range and color indices, therefore, averaging below 0.70. This same blood picture has been observed by others.[8] Because of this almost universal presence of a significant anemia the rôle of hematinics assumes one of importance in the treatment of rheumatoid arthritis. We certainly agree with Hench et al.[11] that there is no rationale to the policy of treating the anemia and allowing the arthritis to take care of itself. Multiple therapeutic agents must be utilized with the emphasis altered to suit the individual patient,[12, 13, 14, 15] but there is hardly a patient with rheumatoid arthritis who escapes a prescription for an hematopoietic agent. Iron is reported effective, usually in large but poorly tolerated dosages,[16, 17, 18] but in the usual amounts iron exerts no benefit.[8, 19, 20, 21] Antianemic therapy with liver injections, either with the crude or purified preparations, in our experience fails appreciably to influence the blood picture. Transfusions, though time consuming, expensive, and occasionally hazardous, provide the only certain method of even temporarily improving this resistant anemia.[13, 17, 15, 19, 22]

Folic acid has recently been shown by Spies et al. to be highly effective in the treatment of Addisonian pernicious anemia in relapse [23, 24, 25, 26] and in

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the treatment of sprue.[26, 27, 28, 29] It is also efficacious in treating the macrocytic anemias of pregnancy [26] and of nutritional deficiencies.[23, 30] It is reported effective in some cases of aplastic anemia following roentgen therapy [31] but apparently has no effect on the hypochromic microcytic anemias due to iron deficiency, myelophthisic or idiopathic states.[24]

Nevertheless, because the anemia of rheumatoid arthritis is, like the disease itself, of unknown etiology, and because it is so resistant to the usual hematopoietic agents, it was thought to be worthwhile to investigate the effect of folic acid as an antianemic factor in patients suffering with rheumatoid arthritis.

Method of Study

Twenty patients with indisputable rheumatoid arthritis were selected for study. Both male and female patients were included in the group and the ages varied from 14 years to 70 years. The average duration of the disease before starting the study was 10.52 years. Nineteen patients had previously received iron and/or liver in the usual therapeutic doses without appreciable benefit; transfusions in some instances had been given at intervals with unsustained correction of the anemia. The patients were divided into two groups consisting of 10 patients each. Group I received five milligrams of folic acid by mouth four times daily and all other hematinics were stopped. Group II received orally five milligrams of folic acid four times daily plus oral ferrous salts in dosages of 200 milligrams of metallic iron per 24 hours.

Initially the peripheral blood was examined in all patients and the determinations of hemoglobin by two methods,[32, 33] a total erythrocyte count, total and differential leukocyte counts, reticulocyte count,[34] sedimentation rate,[35, 36] and hematocrit [33] were determined. These studies were repeated on the fourteenth, thirtieth, sixtieth, and ninetieth days of treatment. Reticulocytes were counted on the second, third, fourth, sixth, eighth, fourteenth, thirtieth, sixtieth, and ninetieth days. Each patient was questioned for the development of toxic manifestations and for the effect of folic acid on the underlying disease symptomatology.

Those patients who failed to exhibit any response were reëxamined for blood loss or excessive blood destruction and gastric analyses were performed for the determination of the presence of free hydrochloric acid. Additional folic acid was then given to these "failures."

Results

The 10 patients with rheumatoid arthritis who received five milligrams of folic acid four times daily for 90 days (Group I) exhibited during the first two weeks an appreciable reticulocytosis, the appearance of a significant number of immature leukocytes and erythrocytes, a rise in the mean corpuscular volume, the color index, and the hematocrit (figure 1). There was a consistent rise in the monocytes. The erythrocytes showed only slight

increase (figure 1). The mean average rise in the hemoglobin in two weeks' time was 0.496 gram with a range of minus 0.14 to plus 1.65 grams; of the 10 patients five (50 per cent) had a definite increase in hemoglobin and an equal number showed no significant response. During the same period the reticulocytes rose from an initial mean average of 1.83 per cent to a mean average of 4.22 per cent with the maximum reticulocytosis appearing on the eighth day of treatment. The mean average hematocrit

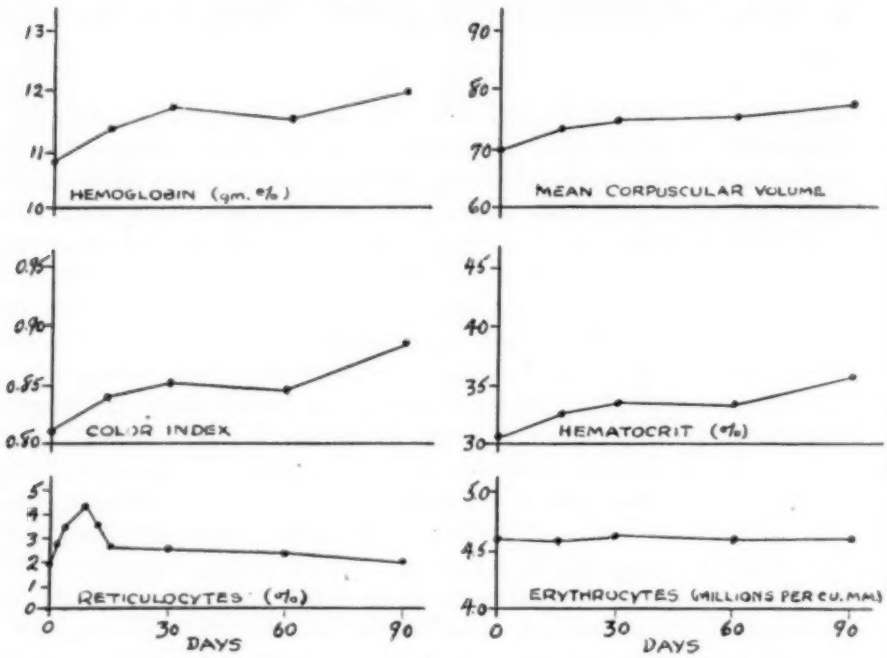

FIG. 1. Mean average blood values of 10 patients—Group I.

rise in two weeks' time was 1.87 per cent and the mean average color index increased 0.029. The erythrocytes rose only 22,000 in an average of 10 patients and the mean corpuscular volume at the end of two weeks was increased from 69.1 to 72.5. The total leukocyte count was not significantly altered and the differential count exhibited no change except for (1) the appearance of immature forms (table 1), and (2) the increase in monocytes from 3.2 per cent to 4.5 per cent.

The over all general improvement in the blood picture noted at the end of two weeks of treatment showed even further gain at the end of one month. The hemoglobin increased during the second two weeks a mean average of 0.375 gram, the hematocrit rose an additional 1.05 per cent, the erythrocytes increased only a mean average of 89,000 but the color index rose an additional 0.015; the reticulocytes exhibited a persistent increase with a mean average level of 2.68 per cent and the mean corpuscular volume again rose

reaching a level of 73.9. The monocytosis persisted at a level of 5.8 per cent. Of special note was the confirmation of the finding of immature forms which in four weeks averaged 1.5 per cent (table 1). At the end of 30 days seven patients (70 per cent) demonstrated a significant rise in hemoglobin and in other blood determinations as noted. Three patients (30 per cent) showed no improvement.

TABLE I

Immature Cells (Groups I and II)

Erythrocyte Series	Initial	14-day	30-day	60-day	90-day
Metakaryocyte (Normoblast)	0	0	1	1	0
Karyocyte (Pronormoblast)	0	4	3	1	2
Prokaryocyte (Erythroblast)	0	5	3	1	0
Karyoblast (Megaloblast)	0	0	0	0	0
Granulocyte Series					
Metagranulocyte (Metamyelocyte)	0	2	5	0	0
Granulocyte (Myelocyte)	0	5	5	4	3
Progranulocyte A (Promyelocyte II)	0	2	6	1	3
Progranulocyte S (Promyelocyte I)	0	0	2	0	0
Granuloblast (Myeloblast)	0	0	0	0	0
Lymphocyte Series					
Prolymphocyte	0	8	4	8	4
Lymphoblast	0	0	0	0	0
Monocyte Series					
Promonocyte	0	0	2	0	0
Monoblast	0	0	0	0	0
Total	0	26	31	16	12

In 60 days the peripheral blood determinations exhibited further alterations. The hemoglobin fell slightly to a mean average value of 11.32 grams. The total erythrocyte count was essentially the same; hence the color index fell to a mean average of 0.852. The hematocrit exhibited a slight rise and the mean corpuscular volume rose to a mean average of 74.5. The reticulocytes were maintained at a level of 2.6 per cent; the monocytes remained at a level of 5.6 per cent and the immature forms were still present in eight cases.

At this point the group was subdivided into those patients who had responded and those who had exhibited no change or were worse. Three patients of the 10 fell in to the latter category and the dose of folic acid was increased in these from 20 milligrams daily to 100 milligrams daily. Those who had shown a response were maintained on the 20 milligram daily dose.

The three patients of this group whose blood values had shown no improvement on the smaller dosage exhibited a startling improvement on the

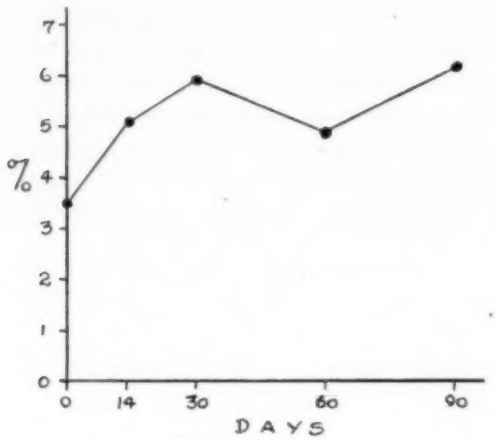

FIG. 2. Monocyte levels—Groups I and II.

larger dose (figure 3). The hemoglobin rose to 12.01 grams, and the erythrocytes remained roughly the same; therefore, the color index rose to 0.85. The hematocrit increased to 34.43 per cent and the mean corpuscular volume went up to 71. The reticulocytes remained at 2.2 per cent and the monocytes rose to 7.1 per cent. On examination of the stained smears the erythrocytes

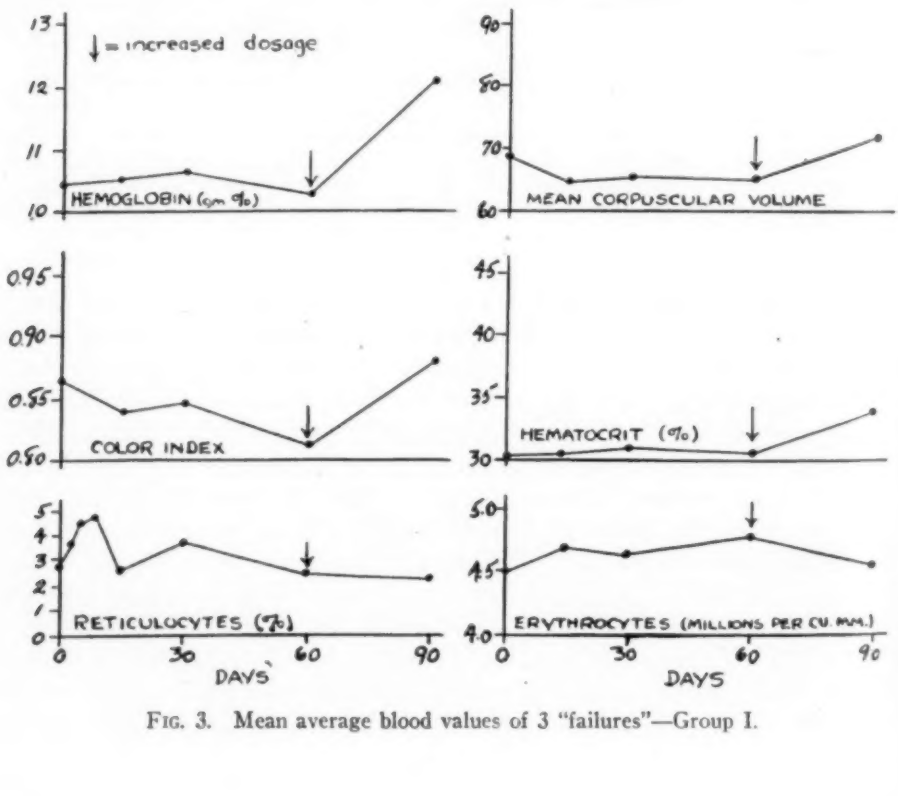

FIG. 3. Mean average blood values of 3 "failures"—Group I.

were rounder, showed less variation in size and shape and the stain was fixed with more uniformity and intensity.

In all 10 patients at 90 days the hemoglobin had risen to a mean average of 11.89 grams, the erythrocytes remained relatively constant, and the color index increased by 0.036 to 0.888. The reticulocytes were still above the initial mean average value at 2.26 per cent and the immature forms were still present in an increased percentage of 0.77 per cent. The hematocrit rose 1.24 per cent to a value of 35.50 per cent and the mean corpuscular volume rose 2.0 to a level of 76.5. Morphologically the red cells were more normal in appearance.

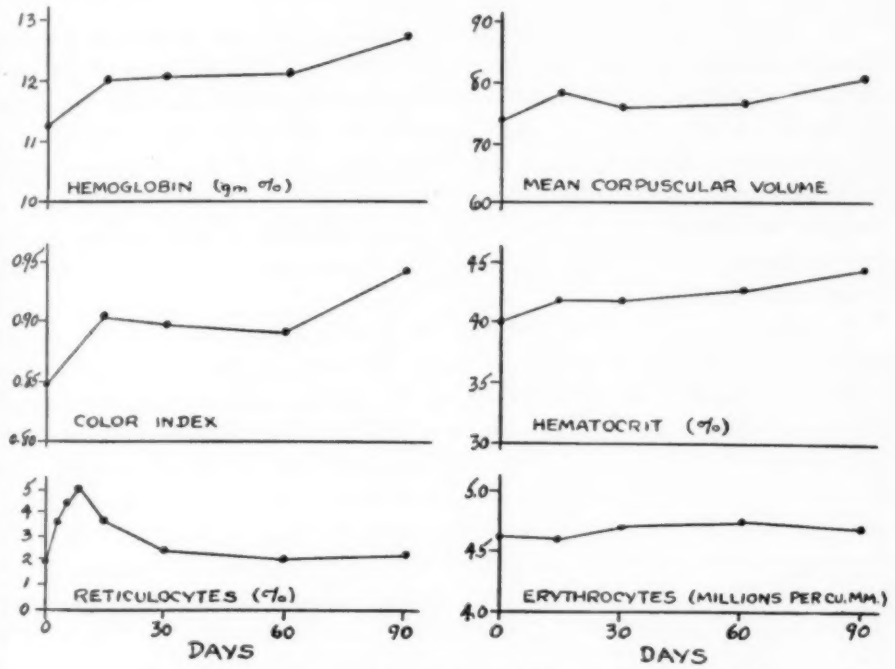

FIG. 4. Mean average blood values of 10 patients—Group II.

The blood picture in 10 patients with rheumatoid arthritis given both folic acid, five milligrams four times daily, and iron salts equivalent to two hundred milligrams of metallic iron daily (Group II) varied from that seen in Group I in that during the first two weeks there was a greater response (figure 4). The hemoglobin rose 0.881 gram, the hematocrit rose 1.92 per cent, on the eighth day the reticulocytes were at a level of 5 per cent and were still elevated on the fourteenth day at 3.54 per cent, the color index gained 0.063 and the mean corpuscular volume rose from 74 to 78. The total erythrocytes decreased a mean average of 9000. The monocytes increased to 5.7 per cent. Of the 10 patients in Group II 80 per cent showed a significant improvement in the blood picture.

Continuation of the treatment for 30 days, however, led to a surprising failure to maintain continued response. Of the 10 patients under consideration eight either failed to improve their blood picture over that of the two week determination or actually there was a decrease in almost all factors. The hemoglobin increased by a mean average of 0.012 gram, the hematocrit fell 0.21 per cent and the color index decreased 0.019 while the mean corpuscular volume fell to 76 from a previous 78. Despite these deflections in the blood values the immature forms remained at a mean average of 1.6 per cent (table 1), the monocytes remained at a mean average of 5.8 per cent, the reticulocytes were still above the initial count at 2.4 per cent and the erythrocytes exhibited no significant change.

The total alterations in the peripheral blood of the two groups of patients in one month were comparable (figures 1 and 4). The patients of Group I made a slow, steady improvement whereas those of Group II made the larger response at 14 days which was not improved but maintained at 30 days. The total hemoglobin rise in Group I was 0.87 gram, that of Group II was 0.869. The total erythrocyte count in Group I was increased by 110,000 and in Group II by 88,000. The color index had increased in both groups by the identical figure of 0.044 and the immature forms were 1.5 per cent and 1.6 per cent respectively.

An additional 30 days treatment in Group II produced a red cell of slightly larger size as evidenced by the increase in the mean corpuscular volume to a mean average of 76.4 and of slightly less hemoglobin concentration as reflected in the color index of 0.884. The hemoglobin increased 0.055 gram to a level of 12.13 grams and the total erythrocyte count rose only slightly. The reticulocytes were still above the initial value at 2.16 per cent. Immature forms appeared less frequently than in the previous determinations and were present in only 0.4 per cent (figure 2). A previously noted monocytosis was of less significance in the mean average and was only 4.1 per cent. Four patients (40 per cent) in the group were classified as failures. The remaining six patients exhibited an appreciable increase in all blood determinations save the total erythrocyte count.

Reëvaluation of the results at the end of two months of treatment revealed that the rises exhibited in the various blood determinations were now appreciably higher than the initial values and that there was a parallelism between Groups I and II with no differences save those based on the higher initial values of the second group over those of the first.

In 90 days the peripheral blood picture in the 10 patients of Group II revealed a progressive rise in the previously indicated determinations. The hemoglobin rose to a mean average of 12.92 grams, an increase of 0.80 gram in the last 30 days. The erythrocytes maintained their constant mean average level of 4.72 million per cu. mm. Consequently the color index rose to a level of 0.944, a rise in one month of 0.060. The hematocrit was observed to be 38.29 per cent, an increase of 1.79 per cent, and the correlating

mean corpuscular volume also rose to 81.2, an addition of 4.8. The reticulocytes remained relatively constant at 2.25 per cent. The monocytes again increased to 6.6 per cent.

It was during this final 30 day period that the patients of this Group II, as was similarly done in Group I, were divided into successes and failures and, as noted, they comprised respectively 60 per cent and 40 per cent of the group. The four failures who had in 60 days of continued therapy shown no improvement were given 100 milligrams of folic acid daily with the results noted in figure 5. Whereas the hemoglobin, hematocrit, color index, mean corpuscular volume were steadily decreasing on the earlier dosages, increas-

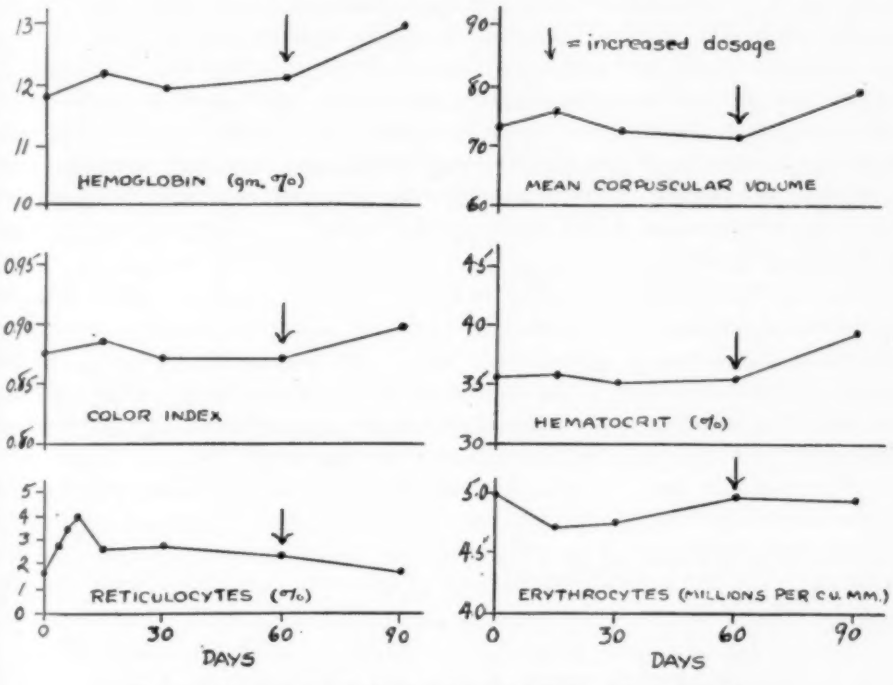

FIG. 5. Mean average blood values of 4 "failures"—Group II.

ing the dosage of folic acid without altering the dosage of iron led to improvement in each of the determined values. In all four of the unresponsive patients (figure 5) the hemoglobin rose to a mean average level of 12.98 grams, the erythrocytes remained constant, and the color index rose to 0.895. The hematocrit increased to 38.45 per cent and the mean corpuscular volume consequently rose to 78.5. The morphology of the erythrocytes revealed a diminished amount of achromia, anisocytosis, poikilocytosis, and the fragmentation was no longer so much in evidence. Immature forms also increased to 0.77 per cent (table 1) and the monocytes again appeared in increased numbers at a level of 7.8 per cent (figure 2).

Every patient classified as a "failure" was subjected to a gastric analysis

and free hydrochloric acid was demonstrated in each. In these same patients urobilinogen levels were normal.

Determinations of the sedimentation rates by means of a modified Westergren method [36] were performed at the intervals already indicated. No alterations beyond those normally expected were observed. Total leukocyte counts were not consistently altered nor were any other specific cells save the monocytes.

Immature cells were first observed on the fourteenth day of treatment and during subsequent examinations they appeared in the differential counts in 10 patients (100 per cent) in Group I and in eight patients (80 per cent) in Group II. Each cell was meticulously identified by means of the criteria established by Dr. Edwin E. Osgood.[37] They appeared at an earlier date in the treatment in Group I and were found in larger numbers than in Group II. At no time during the examinations were stem cells found but cells in all other stages of development were demonstrated. Singularly enough cells belonging to the "pro" stages were found with more frequency than the more mature young forms. Most commonly encountered were cells belonging to the granulocyte series while the prolymphocytes were observed to be next in frequency (table 1).

During this period of therapy in both groups there was a consistent and spontaneously noted generalized sense of well being. However, there was neither objectively nor subjectively any alteration in the progress of the rheumatoid arthritis nor in the degree of functional disability of the patients. No toxic manifestations, untoward effects or discomforts from the therapy were observed in any of the dosages of folic acid employed.

A few additional isolated observations were made. One patient was given 500 milligrams of folic acid per day for five days. A reticulocytosis of 11 per cent was observed on the eighth day and there was a rapid rise to a large degree in the hematocrit, the hemoglobin, the mean corpuscular volume and the color index.

Several patients were given 1.7 milligrams of folic acid daily and there was a response in each patient which was commensurate with this small dosage but which in 90 days showed an accumulative effect. One of this group was given 100 milligrams of folic acid daily for 30 days after having shown a moderate response on the small dosage of folic acid and there was a dramatic improvement in the blood picture identical with those already noted.

Comments

With the facts at hand and the limited number of patients included in this preliminary report any comments must of necessity be of a presumptive nature. It would appear that folic acid in the dosages given exerts an effect on the anemia of rheumatoid arthritis, an effect not observed with any other hematopoietic agent. The peripheral blood picture in rheumatoid arthritis is not only that of a hypochromic, microcytic anemia but the erythrocytes

are sickly in appearance; they are variable in size and shape, stain poorly, are generally small, and have a tendency to fragment easily. Folic acid caused the erythrocytes in the treated patients to be of greater size, of more uniform appearance, of greater staining intensity, and to show less inclination to fragment. Before treatment the morphology of the erythrocytes in many instances resembled the so-called "doughnut cells" and following the use of folic acid the cells were of more uniform character and appeared more amply filled with hemoglobin.

There are no results in any way comparable to those seen in the large and dramatic response to folic acid in pernicious anemia and sprue as shown by Spies et al. On the other hand, the slow, steady, prolonged benefit exerted by folic acid in the anemia of rheumatoid arthritis cannot be disregarded.

At the end of 90 days, 100 per cent of our patients, including the failures treated with increased dosage, enjoyed an improvement in their anemia. The mean corpuscular volume, the hemoglobin, and the color index rose a statistically significant amount in all instances. Of the patients studied those with the most active and vicious rheumatoid arthritis responded poorly on the 20 milligram daily dose and they comprise the majority of the seven failures of both groups.

In our opinion the most remarkable result we encountered was the appearance of young forms in the differential counts made on the peripheral blood. This is a phenomenon not previously observed by one of us (A. B.) in 11 years of continuous observation of the peripheral blood of patients with rheumatoid arthritis under all forms of anti-anemic therapy. Of further interest is the unexplainable occurrence of more cells of the "pro" stages than of the "meta" stages.

Those patients regarded as failures on the 20 milligram daily dose of folic acid responded correspondingly well on increased dosage; which would indicate that the problem of dosage has not yet been solved. Perhaps some patients will benefit from much smaller doses than those employed in this study and we have evidence to show that others require larger amounts of the drug.

The patients of that group given both folic acid and iron did not initially have as profound an anemia as the patients given folic acid alone but the proportionate improvement was almost identical in both groups. This would signify that iron in the dosages given exerted no influence. Increase in the hemoglobin concentration of the erythrocytes was observed without the use of iron (Group I). It would seem fair to conclude, therefore, that the hypochromic anemia of rheumatoid arthritis originates from a cause not intimately associated with the ingestion of ferrous salts and further that folic acid influences this anemia by a mechanism as yet unknown.

In any group of patients with a chronic disease there may exist a simple iron deficiency anemia. Therefore we would hasten to state that iron is not

to be discarded as totally ineffectual in all patients suffering from rheumatoid arthritis. However, it would appear from our results that there is a superimposed process of hematopoietic insufficiency which is not based on inadequate iron in the diet and which does respond to folic acid.

The monocytosis has been carefully included in the reporting of the results because in the differential count that particular cell was the only one observed to undergo any percentage change. The significance of this interesting occurrence cannot be stated. The complete ineffectiveness of folic acid in influencing the underlying disease process in the time involved would suggest that the increase in the number of monocytes bears no relation to recovery or repair and that possibly this phenomenon is merely a side effect in the pharmacological action of folic acid.

The ineffectiveness of crude liver in correcting the anemia of rheumatoid arthritis and the evident benefits of folic acid appear to divorce these substances in their pharmacological action. It has been observed that liver will cause an adequate response in pernicious anemia in relapse or in sprue although assays reveal only small ineffective amounts of folic acid in the extract. The proponents for the specificity of folic acid in the treatment of macrocytic anemias suggest that there are additional liver substances which release bound or stored folic acid already in the body. Our results would tend to discredit this theory or at least suggest that there is a great variation in the effective dosages of folic acid in different diseases.

Additional studies with increased dosage are being carried out and as further light is thrown on this apparently powerful bone marrow stimulant it may be determined that folic acid will play a significant rôle as one of the multiple therapeutic agents used in the treatment of this vicious, debilitating, and disabling disease.

Conclusions

1. Folic acid improved the blood picture in 100 per cent of a group of 20 patients with rheumatoid arthritis. There was an increase in the mean corpuscular volume, the hematocrit, the hemoglobin, the color index, and the morphology of the erythrocytes without comparable rise in the total erythrocyte or leukocyte counts.

2. Folic acid caused the appearance in the peripheral blood of immature leukocytes and erythrocytes of all categories save those of the plasmacyte series, a phenomenon heretofore not noted with any other antianemic therapy in rheumatoid arthritis.

3. Iron did not enhance or detract from the hematinic effectiveness of folic acid in those patients studied.

4. Folic acid produced an appreciable monocytosis.

5. No improvement was noted in the underlying disease, rheumatoid arthritis, nor were any toxic manifestations observed in any of the dosages employed.

6. The dose of folic acid required to produce a response apparently varies widely.

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THE HEART RATE IN MALARIA; A REVIEW OF NINETY CASES *

By SHERMAN M. MELLINKOFF, Capt., M.C., A.U.S., and JOHN R. HIGGINS, Capt., M.C., A.U.S.

MOST textbooks state that the typical malaria patient exhibits chills, fever, and tachycardia.[1, 2, 3, 4, 5] This clinical triad is frequently helpful in the differential diagnosis that runs through the physician's mind when he first sees a patient in a malarious zone. Among army personnel in certain regions of Asia, for example, it is common to see an acutely ill, prostrated man with chills and fever, while the physical examination gives no clue to the diagnosis except the heart rate. On the basis of probability in this particular locality, when there is a relative bradycardia one thinks of the pre-icteric stage of hepatitis first and typhoid fever second. In both of these diseases the white count is ordinarily low. At an Asiatic military hospital we have been occasionally surprised, however, to find that a patient with fever, relative bradycardia, and leukopenia turns out to be ill with malaria.

Bradycardia is not usually considered to be a feature of malaria, although some investigators have pointed out this important phenomenon.[6, 7, 8] Indeed Hughes and Bomford maintain that "relative bradycardia was a principal feature of the disease (malaria) as seen by us in West Africa." [9] The British Army considers that "malaria may simulate any acute or subacute fever and may be called on this account 'The Great Mimic' among diseases." [10]

We have reviewed the records of our malaria patients to investigate the relationship between pulse rate and fever. Our findings indicate that the pulse rate covers a wide latitude in malarial fevers, and ranges from the tachycardia seen in the ordinary septic diseases to the bradycardia of typhoid.

All patients definitely diagnosed as malaria during the months of January through the first part of September, 1946, are included in the present study, with the exception of four patients with falciparum malaria whose charts were lost to us through transfer to a higher echelon. In all 90 cases the diagnosis was made by identifying the parasite in thin or thick blood smear. There were 85 patients with *Plasmodium vivax*, two with *Plasmodium falciparum*, and three with *Plasmodium malariae*. Most of the infestations were traceable to the Philippine Islands, the appearance of clinical symptoms having been delayed by prophylactic doses of atabrine. The latter were discontinued at various times ranging from September, 1945, to April, 1946. One patient with quartan malaria contracted the disease in Okinawa, and six cases were acquired in Korea—two due to each of the three types of plasmodia. The remainder of the cases were contracted in the Philippine Islands.

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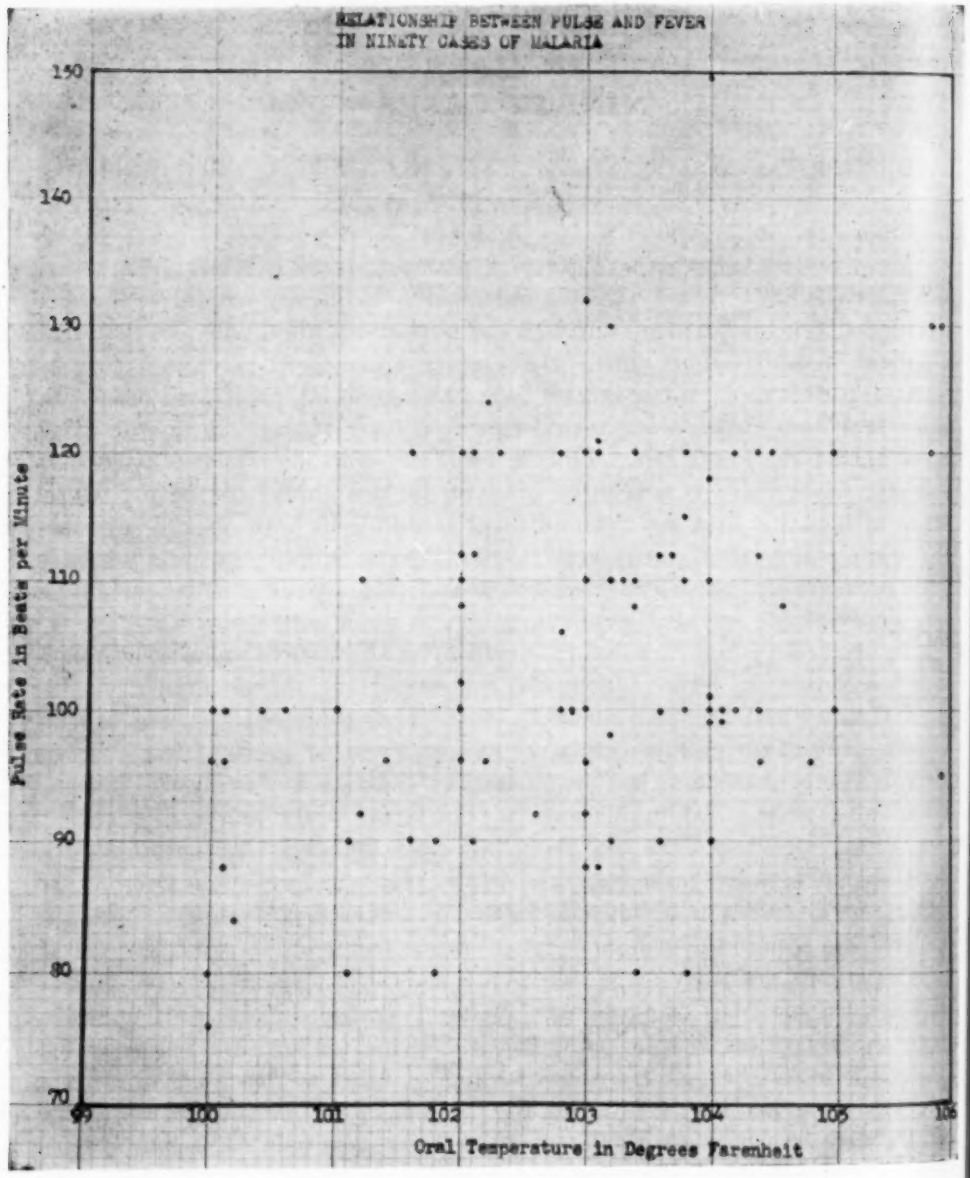

FIG. 1.

Most of the patients had at least one full-blown chill in the hospital before the diagnosis was made. A few were admitted in the decline of an initial chill, and diagnosis was made and therapy instituted before a second chill made its appearance. Since this paper is primarily concerned with the clinical picture of the patient when first seen by the doctor, the relationship between the highest fever and the highest pulse rate on the first hospital day is

recorded. These peaks represent the height of a malarial paroxysm in the majority of patients. In some they represent a fever seen at some time during the subsidence of a paroxysm. About one fourth of the patients, however, had two or more chills in the hospital. An analysis of those chills indicates that the data contained here are not artefacts created by the in-

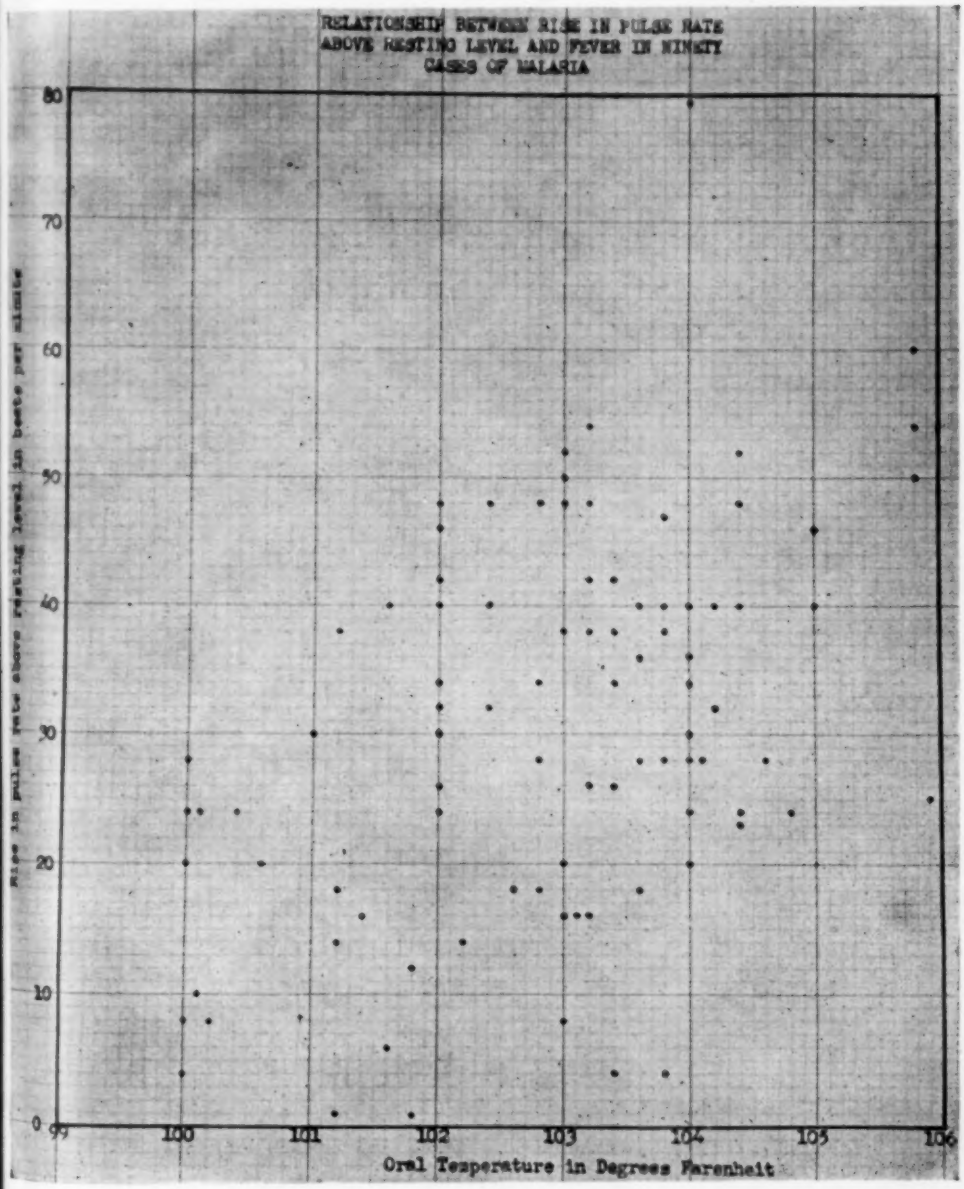

FIG. 2.

cidents of hospital admission, but rather are characteristic of all paroxysms observed.

There were no deaths or permanent disabilities. All patients were treated with atabrine alone, or atabrine in conjunction with quinine. In 13 patients there was an associated disease, but in no case was the secondary illness of a type or severity to change substantially the temperature and pulse. Examples are coryza, ascariasis, and non-specific penile ulcer.

One patient was 31 years of age, and the others were from 18 to 24 years old. In eight cases there was no chill, although in these eight cases the ob-

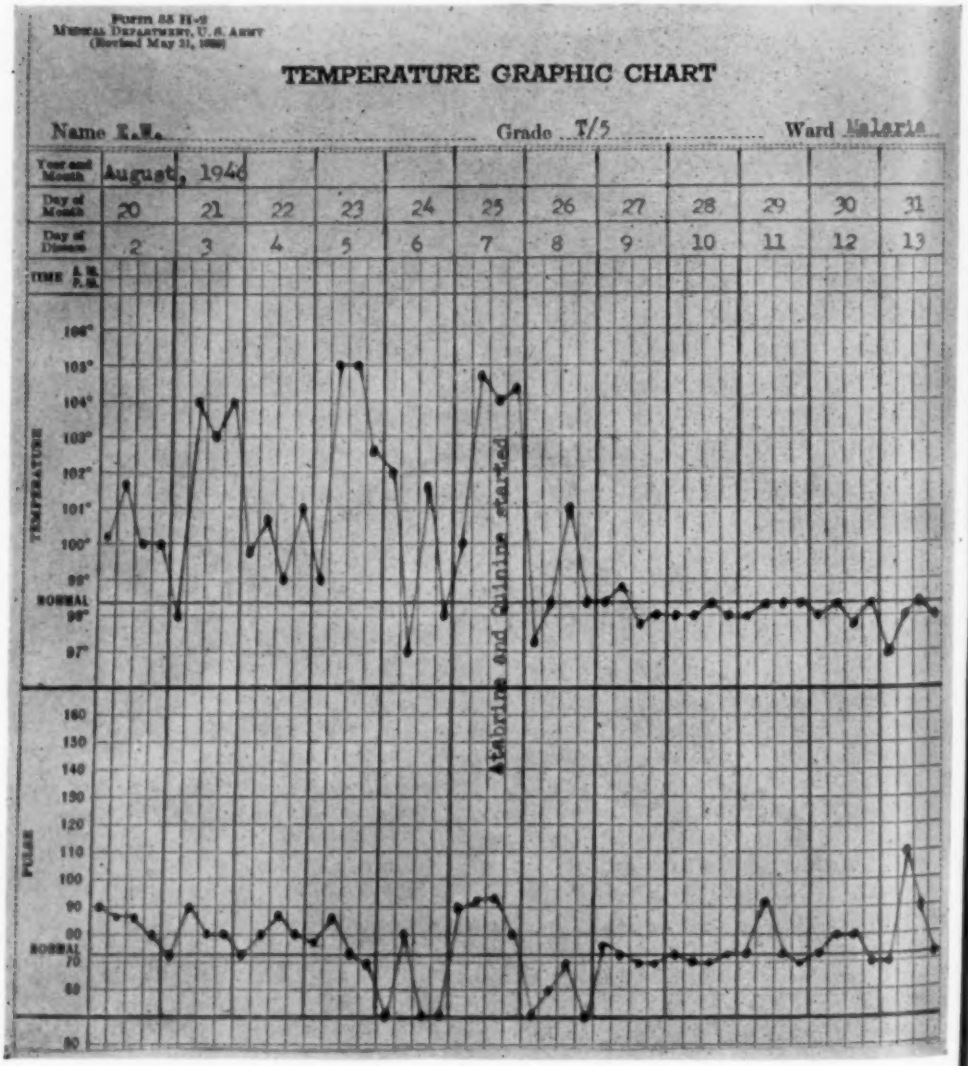

FIG. 3.

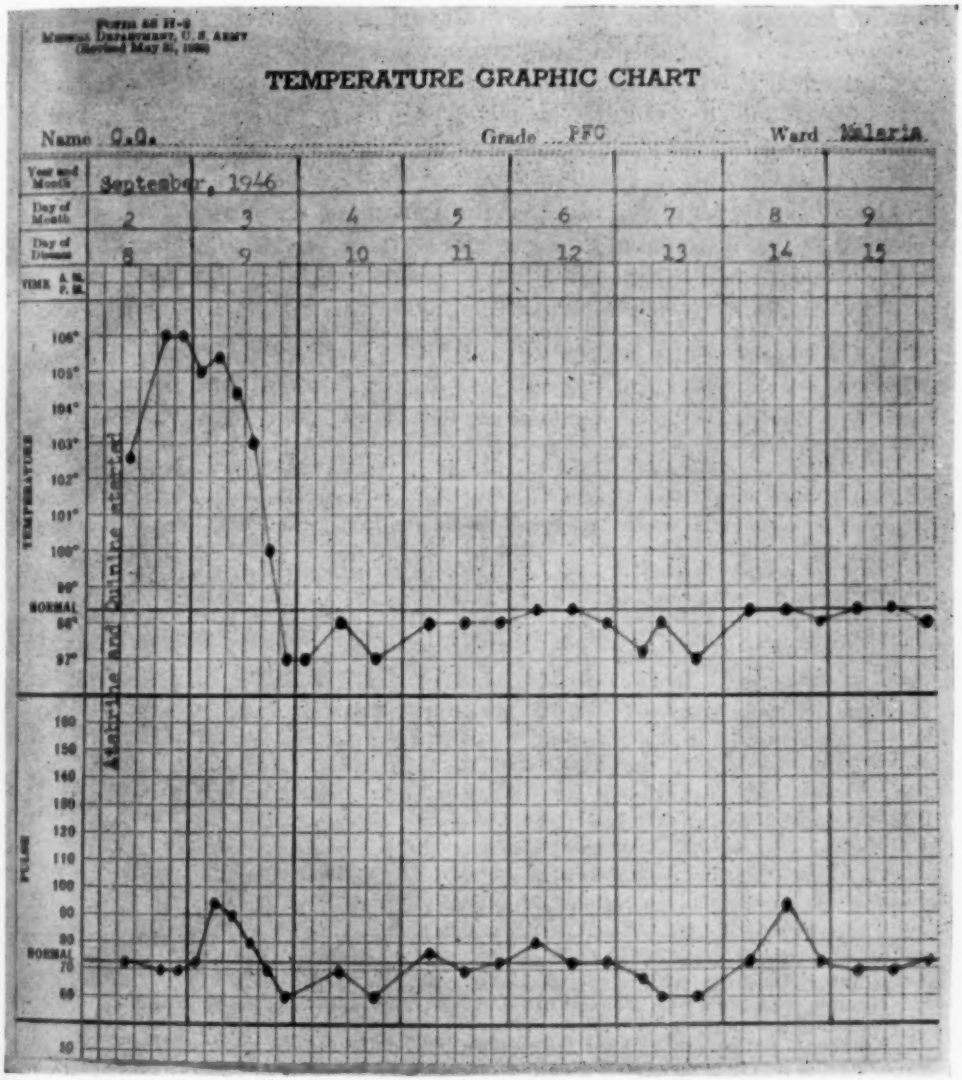

FIG. 4.

served fever ranged from 102.8 to 104° Fahrenheit by mouth. In 29 patients the degree of malaise was surprisingly mild. These men would complain of "feeling hot," and almost only if specifically asked would admit "a little headache" and "a few aches in the bones." The remaining 61 patients had varying degrees of more severe malaise. One of the cases of falciparum malaria had extreme prostration, a pounding headache, photophobia, pronounced nuchal rigidity, lancinating pains in the thighs, a feeling of impending death, and marked irascibility. Examination of his spinal fluid was negative. Thirty-nine patients complained of nausea, and 14 of those had

more or less severe vomiting. One of the malignant tertian cases had severe hematemesis. Five patients had diarrhea, one with 20 bowel movements a day, that cleared with antimalarial therapy alone. No parasites were found in the stools, and stool culture was negative in every instance. The distribution of the white blood cell counts was as follows: (1) Between 2900 and 5000: 12 patients. (2) Between 5000 and 9000: 39 patients. (3) Between 9000 and 12,000: six patients. In the remainder no white blood count is recorded. The differential white counts were usually within normal limits, with an occasional eosinophilia, an occasional relative lymphocytosis or monocytosis, and rarely a relative preponderance of polymorphonuclear leukocytes.

TABLE I

Relationship between Pulse and Fever in 90 Cases of Malaria

Temp.	Number of patients with pulse rate of						No. patients with rise above resting pulse of					
	70–80	81–90	91–100	101–110	111–120	121–150	0–10	11–20	21–30	31–40	41–50	51–80
100–100.9	2	2	6	0	0	0	4	2	4	0	0	0
101–101.9	2	3	3	1	1	0	3	4	1	2	0	0
102–102.9	0	1	6	4	6	1	0	3	4	6	5	0
103–103.9	2	4	6	6	7	3	3	5	4	8	6	2
104–104.9	0	1	8	3	5	1	0	1	8	6	1	2
105–106	0	0	2	0	2	2	0	0	1	1	2	2

Number of patients with temperature above 102.9 and pulse below 101.....23 or 25.5%
Number of patients with temperature above 102.9 and pulse below 91..... 7 or 7.7%
Number of patients with temperature above 102.9 and pulse-rise above resting level of less than 31.....22 or 24.4%
Number of patients with temperature above 102.9 and pulse-rise above resting level of less than 21.....10 or 11.1%

By reference to the accompanying graphs and table one can observe the degree of cardiac acceleration in relation to the fever. The pulse recordings represent the greatest relative tachycardia observed with the height of each initial fever. After subsidence of all fever and malaise, the resting pulse rate was determined in each case by observing the consistent pulse rate an hour after the patient had awakened after a good night's sleep. The interval hour comprised bed rest. In the second graph the height of each fever is plotted against the maximum rise above the resting pulse rate in each case. By comparing the two graphs it can be seen that the degree of tachycardia or relative bradycardia was not a factor of the resting pulse rate, but indeed represented

a true variation in the cardiovascular response to fever. The variation was very wide and indicates that tachycardia as well as relative bradycardia can occur.

To illustrate the instances of relative bradycardia the temperature and pulse graphs of two patients are presented:

Patient "E. W." was a 20 year old white infantryman who entered the hospital on August 20, 1946 complaining of fever, lassitude, headache, and "dizziness" of 24 hours' duration. Onset had been gradual, and there were no chills. Physical examination was entirely negative except for the fever. Blood pressure was 120 mm. of mercury systolic and 60 diastolic. White blood cell count was 2900, with 68 per cent polymorphonuclear leukocytes, 25 per cent lymphocytes, and 7 per cent monocytes. The pulse rate at no time rose above 91, while three tertian fevers were observed, reaching respectively 104, 105, and 104.8° Fahrenheit by mouth. It was interesting that when the patient was afebrile and his activity confined to lavatory privileges, there was as much rise in pulse rate as there was with the fever. *Plasmodium vivax* was discovered in thin blood smear during the third paroxysm, and routine antimalarial therapy was instituted. On the twelfth hospital day the following observations were made: When the patient stepped off and on a chair 16 inches high 15 times in four minutes the pulse rate rose from 72 to 118 beats per minute. When this procedure was carried out 20 times in eight minutes, the pulse rate rose from 72 to 122 beats per minute. In short, a relatively small amount of exercise was capable of producing a greater cardiac acceleration than was a fever of 105°.

Patient "C. G." was a 19 year old white private in the military police. One week prior to admission he had developed a pounding occipital headache and stiffness in the neck. Five days before admission he had a severe chill with shivering and generalized malaise. This was followed in four hours by a profuse diaphoresis. In the following five days he had a similar paroxysm every day, and on the eighth day of his illness he was admitted to the hospital just after a relatively mild chill. Physical examination was entirely negative except for fever and prostration. Blood pressure was 120 mm. of mercury systolic and 50 diastolic. Blood smear immediately revealed typical quartan parasites and atabrine and quinine were given at once. One half hour later the patient had a second chill, with shaking and severe headache. By reference to the temperature graph it can be seen that when the fever was 106° the pulse rate was 70, while the height of the pulse rate was only 95 with a fever of 105.4° On the eighth hospital day the patient rested two hours in bed and then stepped on and off a chair 16 inches high 15 times in four minutes. The pulse rate rose from 70 to 115 beats per minute.

Summary and Conclusions

1. Ninety cases of malaria are reviewed with particular attention to the relationship between pulse rate and fever.

2. Malarial fevers may be accompanied by all degrees of cardiac acceleration, ranging from the tachycardia seen in many bacterial infections to the bradycardia of typhoid fever.

3. In this series of cases about one fourth of the patients had a relative bradycardia.

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CASE REPORTS

AN UNUSUAL CASE OF VENTRICULAR TACHYCARDIA *

By S. Demarest Beers, M.D., and Clarence E. de la Chapelle, M.D., F.A.C.P., *New York, N. Y.*

Case Report

A 57 year old white male was admitted to this hospital with the chief complaint of palpitation of 10 hours' duration.

The patient gave a history of attacks of palpitation for some 20 years lasting from a few minutes to a few hours. They were accompanied by weakness and dyspnea. The interval between the attacks varied from one to six months. The attacks were apparently initiated by over-eating and excitement. During the year prior to admission he had two or three episodes which lasted for 24 hours or longer. The attacks usually began and ended abruptly and spontaneously. Frequently he was able to terminate the attacks by stretching his arms and twisting his body. Carotid sinus pressure or orbital pressure was never tried.

He gave no history of chest pain, exertional dyspnea, orthopnea, nocturnal paroxysmal dyspnea or peripheral edema. No history of rheumatic fever or heart disease could be elicited.

The patient was seen in the Cardiac Clinic 12 days prior to his present attack of palpitation at which time his blood pressure was 196 mm. Hg systolic and 108 mm. diastolic. There was a short, low-pitched systolic murmur audible at the apex; the rhythm was regular with occasional premature contractions. An electrocardiogram taken February 26, 1945 (figure 1), about three weeks before the present episode, showed T_1 and T_2 diphasic, P_2 and P_3 notched, and a rate of 75 per minute.

His present attack of palpitation began 10 hours prior to admission and could not be terminated by him.

Physical examination on admission March 17, 1945. Temperature 100.4° F., respirations 24; pulse 144; blood pressure 110 mm. mercury systolic and 80 mm. diastolic.

He appeared dyspneic and slightly cyanotic. An injected pharynx was noted. Wheezes and rhonchi were heard throughout both lung fields and some moist râles at both bases. The point of maximal impulse was in the fifth left intercostal space, midway between the anterior and mid-axillary lines. No thrills were palpable. The heart sounds were of good quality, and no murmurs were heard; ventricular rate was 200; pulse rate, 168. The liver was palpable one finger's breadth below the right costal margin. There was no peripheral edema.

Laboratory data: Hemoglobin 12.0 gm. Red blood cell count was 3,900,000. White blood cell count was 9000 with polymorphonuclears 72 (15 immature), and lymphocytes 28. Wassermann reaction was negative. Urinalysis showed a trace of albumin and four to six white blood cells per high power field. The erythrocyte sedimentation rate was 6.0 mm. in one hour.

* Received for publication December 7, 1945.
From Lenox Hill Hospital, New York, N. Y.

An electrocardiogram (figure 2) taken on the day of admission (March 17, 1945) showed ventricular tachycardia with a rate of 160, T_1 inverted, Q_2 and Q_3 deep, and a left axis deviation. For the first two days he received 0.4 gm. quinidine sulfate per os every two hours for a total of 5.4 gm. Despite this the ventricular tachycardia of 160 persisted. On the afternoon of the second day he was given 10.0 c.c. of 10 per

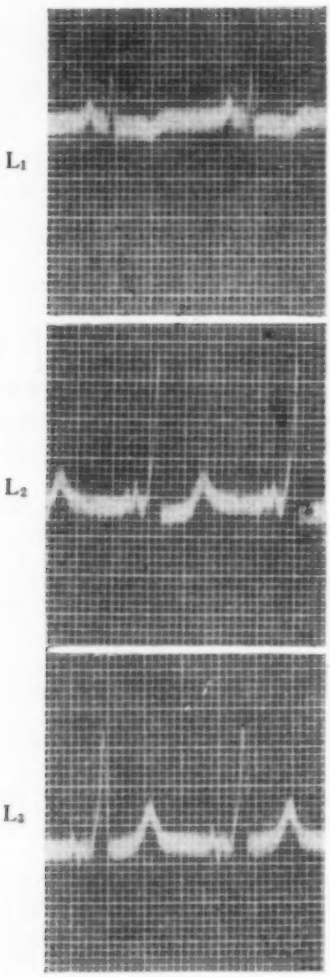

FIG. 1. Electrocardiogram taken February 26, about three weeks before attack.

cent magnesium sulfate intravenously but there was no change in the rate. That same evening 20.0 c.c. of 10 per cent magnesium sulfate were repeated but with no effect. During his third and fourth hospital days the patient received 1.0 gm. potassium chloride by mouth every two hours for a total dose of 8.0 gm. On the third day, together with the potassium chloride, he received 20.0 c.c. of 25 per cent magnesium sulfate intravenously, but the ventricular rate remained at 185. On the fourth day his ventricular rate fell to 124 but rose to 168 that same day. Electrocardiograms taken on these two days were similar to the tracing taken on admission. After his

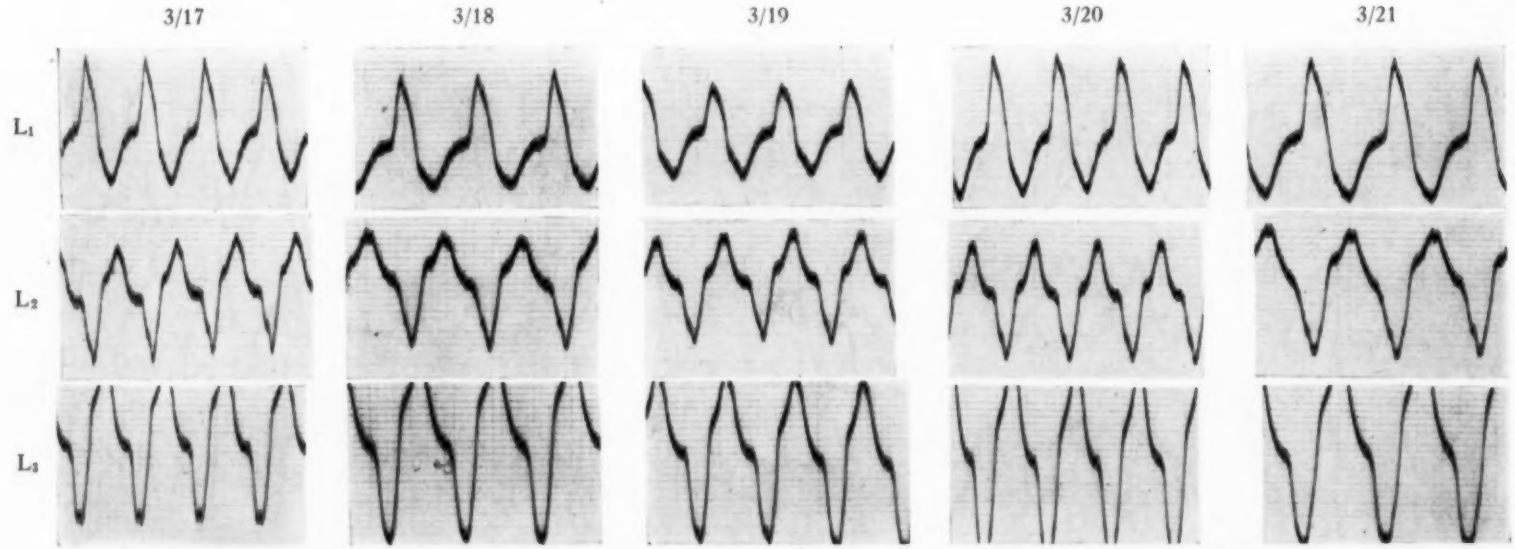

FIG. 2. Electrocardiograms taken on day of admission and on successive days, showing ventricular tachycardia.

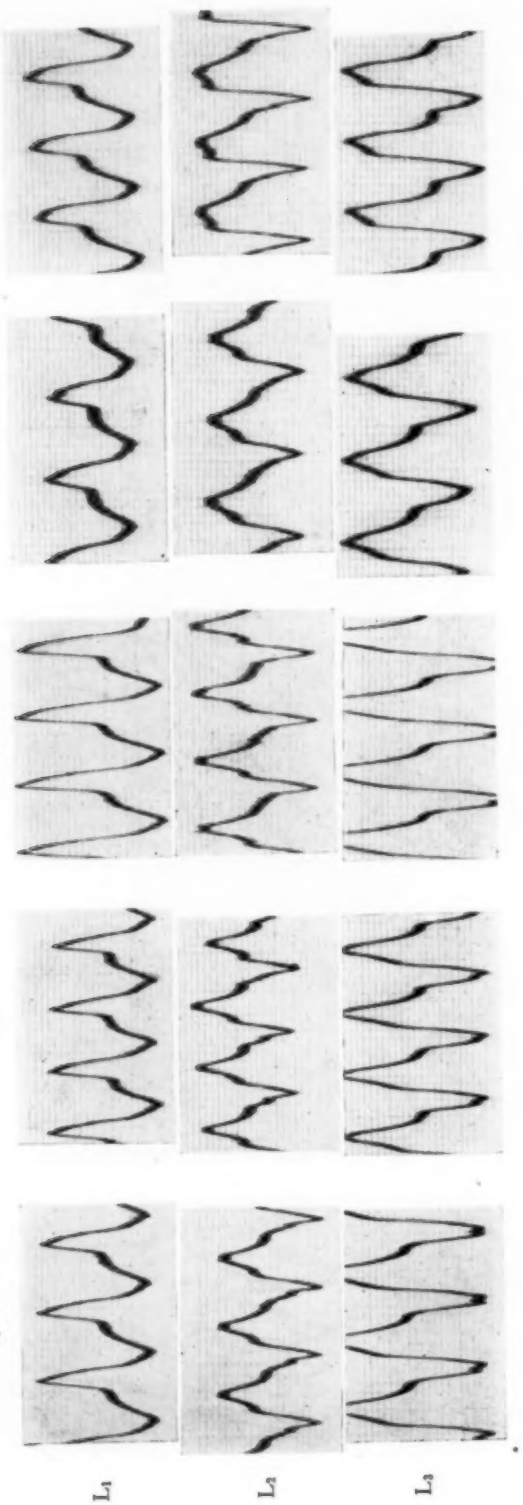

FIG. 3. Successive electrocardiograms during persistence of the attack. Ventricular tachycardia still present.

last dose of potassium chloride he was put back on quinidine sulfate, 0.6 gm. every two hours. This was continued until the afternoon of the fifth day when it was discontinued because of tinnitus and dizziness. At this time he had received a total of 7.5 gm. of quinidine sulfate, but the ventricular tachycardia persisted. For the rest of the day and the morning of the sixth day he again received 1.0 gm. potassium chloride every two hours for a total of 6.0 gm. On the sixth day the erythrocyte sedimentation rate was 42 mm. in one hour; the white blood cell count was 8000 with polymorphonuclears 72 (11 immature); lymphocytes 22; monocytes 4; and eosinophiles 2.

On the afternoon of the sixth day it was decided to give him quinidine intramuscularly as suggested by Riseman, and associates.[1, 2] The first dose of 0.45 gm. (3.0 c.c.) was given at 3 p.m. when the heart rate was 160. At 5:30 p.m. the rate was 158 and since no toxic symptoms had developed a second dose of 0.3 gm. (2.0 c.c.) was given but without effect on the rate. On the seventh day it was decided to give him an intensive course of quinidine intramuscularly. Accordingly he was given a total of 2.75 gm. in doses of 0.45 gm. (3.0 c.c.) at intervals of approximately two hours. During this time the rate dropped to 122 but an electrocardiogram (March 22, 1945) showed that ventricular tachycardia persisted (figure 3). At the request of a member of the attending staff 1.0 c.c. of eutonon was given intravenously at 5:45 p.m. but with no effect (March 23, 1945, figure 3).

During the first week the patient's temperature per rectum showed daily fluctuations from 98.8° to 100.4° F. with a spike to 101.0° on the fourth day and another of 102.2° on the seventh. His respirations varied from 18 to 32. The pulse deficit varied from 10 to 62 beats per minute.

Throughout the eighth day the intramuscular use of quinidine was continued since no signs of cinchonism had developed. He received 4.75 gm. of quinidine during the day and that night had two doses of atropine 0.4 mg. each. His rate dropped to 120, rose to 158, and again fell to 120, but the ventricular tachycardia persisted. On the ninth and tenth days he received quinidine intramuscularly in total daily doses of 4.0 gm. and 6.75 gm. during which time the ventricular rate fell to 100. Ventricular tachycardia persisted according to an electrocardiogram taken at this time (March 25, 1945, March 26, 1945, figure 3). Toward the end of the tenth day signs of cinchonism appeared and therapy was discontinued. On the eleventh day Eutonon was again used at the request of one of the attending staff. Two doses of 2.0 c.c. each were given intravenously at 3 p.m. and at 5:30 p.m. but without any effect (March 27, 1945, figure 3). On the twelfth day the ventricular rate was 164 at 8:50 a.m. but at 10:15 a.m. it was found to be 96. An electrocardiogram revealed a normal sinus rhythm, rate 100 per minute (figure 4).

During the second hospital week minimal signs of cardiac failure developed in the form of moist râles at both lung bases. This was controlled by two intravenous injections of mercupurin at three day intervals. Four times during the first two weeks of hospital stay the patient had to be catheterized. This was attributed to the fact that the patient was on complete bed rest and had benign prostatic hypertrophy. During the second week the temperature remained below 100.0° F. except for a single spike to 102.6° on the eleventh hospital day. Respirations varied between 18 and 28.

For the next 16 days he continued to have a normal sinus rhythm with a ventricular rate that varied between 66 and 84. Respirations were normal and the temperature was never above 99.6° F. per rectum. The white blood cell count varied between 6300 and 9000 with a normal differential. The erythrocyte sedimentation rate reached a peak of 100 mm. in one hour by the twenty-second hospital day. Physical examination during this time was negative except for pulmonary rhonchi and wheezes. On the twenty-eighth hospital day and 17 days after the tachycardia had ceased, ventricular premature contractions were observed, and the patient was

put on quinidine sulfate 0.2 gm. three times a day per os. Two days later, shortly after midnight, ventricular tachycardia recurred and persisted for 30 hours during which time he received quinidine sulfate 0.2 gm. three times a day per os. The next morning the ventricular rate dropped to 90 with a normal sinus rhythm. Following this attack the dose of quinidine sulfate was increased to 0.2 gm. four times a day per os.

For the next five days the patient was asymptomatic and was allowed to sit up. On the thirty-fifth hospital day ventricular premature contractions were again noted and about 10:30 p.m. that night the patient noticed the onset of tachycardia. The next day he received 0.2 gm. of quinidine after which all medication was discontinued.

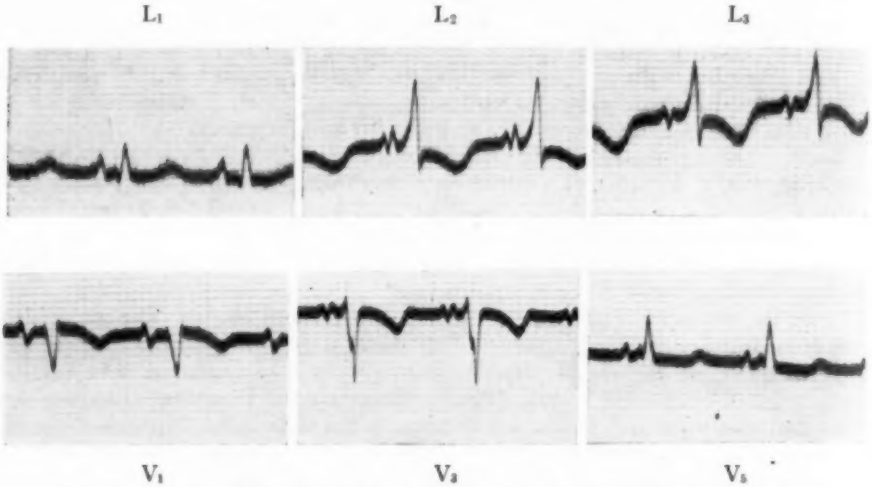

FIG. 4. Electrocardiogram taken on March 28, during an interval between attacks of tachycardia.

Twenty-six hours after the onset of this attack the rate dropped to 70 and became slow and regular. No electrocardiogram could be taken during this attack owing to mechanical difficulty. Following this episode the patient was allowed up gradually and finally discharged 40 days after admission.

Electrocardiograms taken between the three short episodes of tachycardia showed notching of P in the standard leads as well as depression of the ST segment and diphasic T waves in Leads II and III (figure 4). These T waves gradually became upright, but the pattern was repeated after each bout of tachycardia (figure 3).

The patient was considered to have sustained a coronary occlusion with myocardial infarction. For this reason the intravenous use of either quinine or quinidine was avoided because of a previous unfortunate experience some years ago on the part of one of us (C. E. C.) and despite more recent reports of favorable responses.[3]

SUMMARY

An unusual case of ventricular tachycardia is reported which persisted for 12 days in spite of intensive therapy and which had a spontaneous return to normal sinus rhythm. The underlying structural disease was considered to be myocardial infarction.

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SO-CALLED "INFARCTION TYPE" ELECTROCARDIOGRAPHIC CHANGES FOLLOWING PAROXYSMAL TACHYCARDIA *

By Sylvan D. Solarz, Major, M.C., A.U.S., *Chicago, Illinois* †

The problem of the early diagnosis of myocardial infarction in the age group of those serving in the armed forces has been difficult. In the early days of the emergency the diagnosis was not made promptly because of the lack of experience with this disease in relatively young men. The easy availability of electrocardiograms has made the diagnosis more certain in many instances, but at the other extreme there has been the tendency to err on the conservative side and to read too much into the tracings. Then too, relatively rare conditions have been called infarction without careful analysis with the resultant labelling of the patient as a "coronary case" with the unfavorable prognostic implications of that disease.

In recent years there have been several reports of instances of prolonged inversion of the T-waves in the electrocardiogram following bouts of paroxysmal tachycardia.[1, 2, 3, 4] The very great importance of differentiating this condition from myocardial infarction has been stressed by the writers.

Recently a 40 year old major was transferred to this general hospital from another hospital because of the deactivation of that installation. The transfer diagnosis was "recent infarct of the myocardium with nodal tachycardia secondary to the infarction, onset January 26, 1946." On arrival here an electrocardiogram was obtained (figure 1 C, March 5, 1946); it was normal. Because of the relatively short period of time that had elapsed since the onset of the disease and the finding of a normal record the patient was referred to the author for consultation. The following history was obtained.

Case Report

The patient was admitted to another Army general hospital at 8:30 a.m. January 29, 1946 complaining of a rapid heart action, inspiratory difficulty, weakness, and a "washed out" feeling of three days' duration.

The past history was negative. The patient had always been healthy, was a hard driving, forceful type of individual and, in the Army, he had been working in a similar manner.

The family history revealed that the patient's father, aged 69, had angina pectoris. The patient's mother and son had hay-fever and asthma.

* Received for publication November 1, 1946.

† From the Cardiovascular Section, Wakeman General Hospital, Camp Atterbury, Indiana. Present address: Michael Reese Hospital.

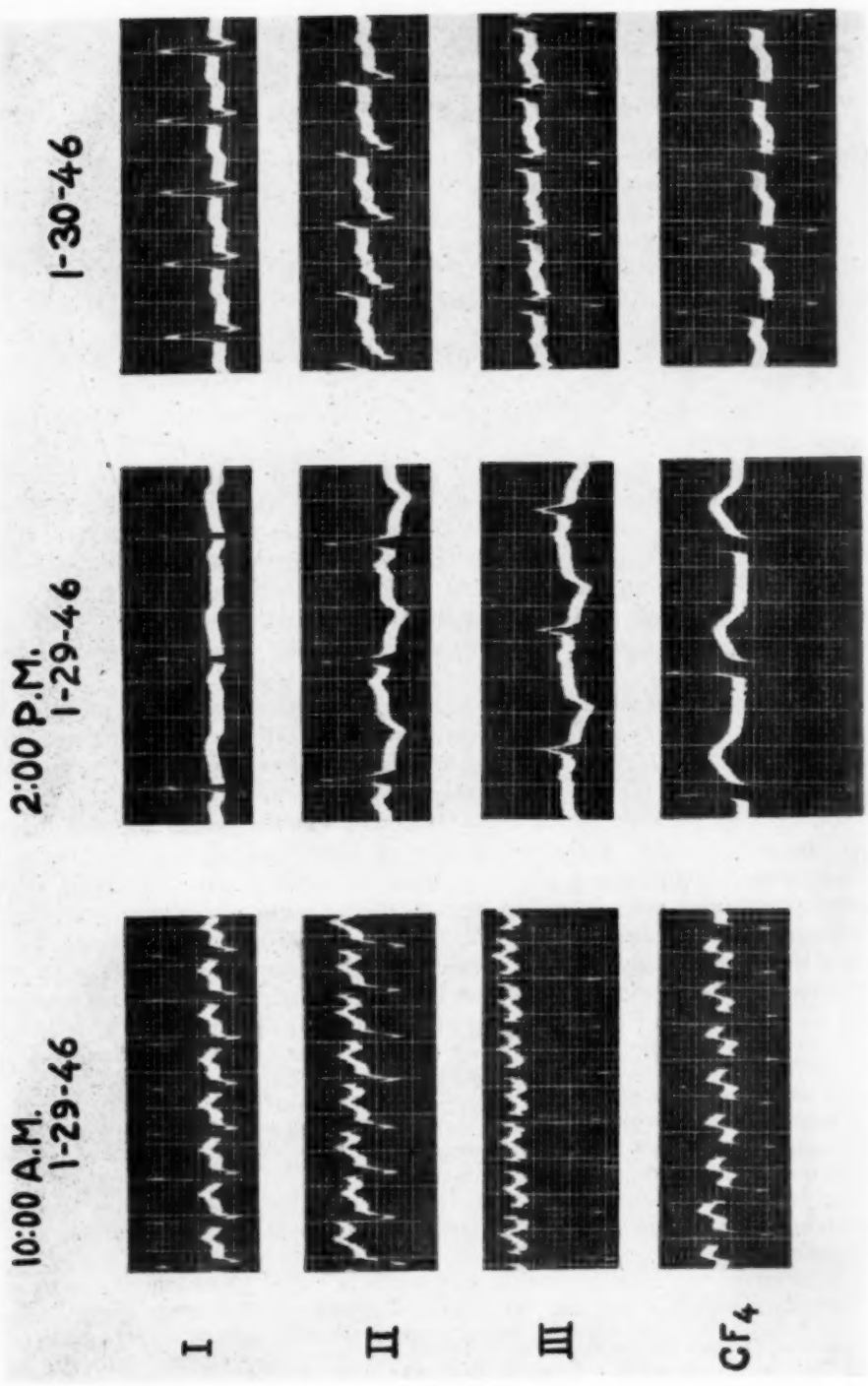

FIG. 1 A. Discussed in text. Note the characteristic bizarre T-waves especially marked in tracing on January 31, 1946.

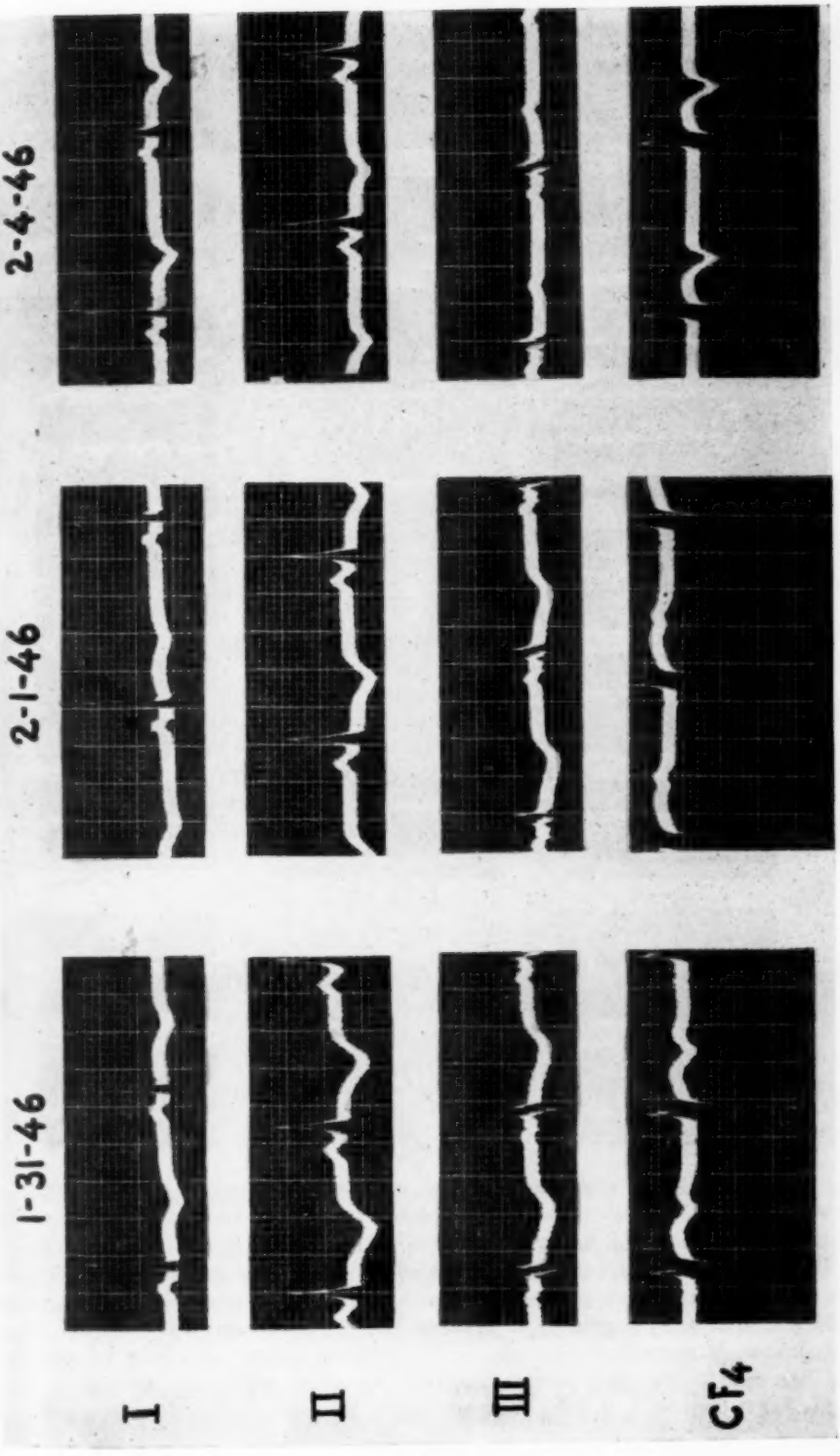

FIG. 1 A (*Continued*).

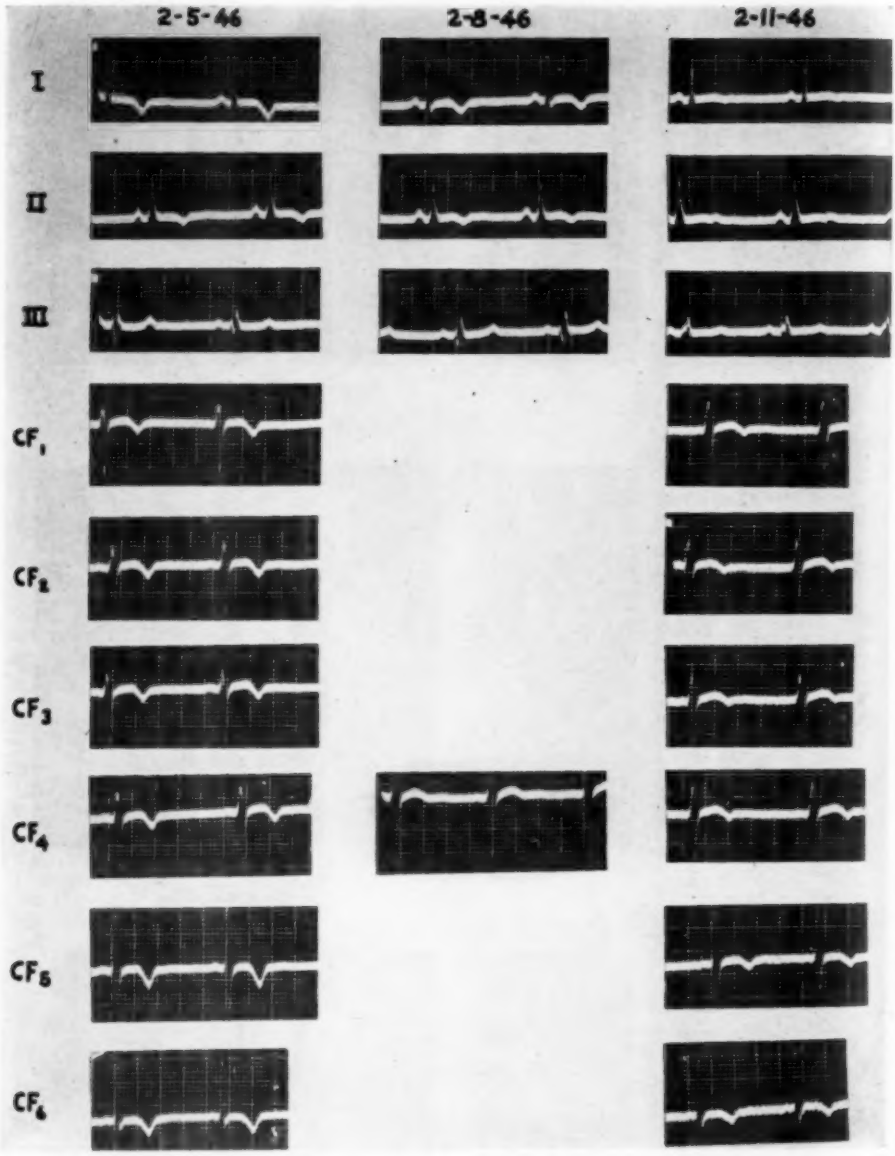

FIG. 1 B. Continuation of figure 1 A. Note the absence of QRS changes in all leads. Discussed in text.

During the week preceding the onset of his illness the patient had been flying cross country, piloting his own plane, from one post to another, working very hard and long hours. On the evening of January 26, 1946 the patient was in New Orleans. While leaving a restaurant after dinner he suddenly became aware of an extremely rapid heart beat. His gait became unsteady, his arms felt heavy, he became dizzy, and his heart "felt as if it were jumping out of his chest." On deep inspiration he

felt a knife-like pain between his shoulder blades and retrosternally. Because of the pain he was forced to limit his respiratory efforts to short, shallow respirations.

The patient was able to return to his hotel without aid. He thought he had a digestive disturbance so he induced vomiting and took an antacid without influencing the heart rate or the inspiratory pain. There was no crushing chest pain at any time. The patient was able to lie flat in bed without difficulty and eventually fell asleep. He awakened about 8:30 a.m. on January 27 and felt "washed out." There was no pain, and the patient was no longer conscious of the rapid heart rate. While eating a light breakfast he began to sweat profusely and once more became aware of the fluttering sensation in his chest. He returned to bed and felt better. After spending the day quietly in bed he was able to walk six blocks to a restaurant that night. He felt weak and was conscious of a rapid heart action, but the fluttering sensation had disappeared. After a light meal he returned to bed and slept well.

On the morning of January 28 the patient felt well enough to fly his plane a distance of approximately 500 miles in three hours. While in the air he felt normal. After landing at his destination he transacted some business for about one-half hour when he again became aware of the fluttering sensation. Nevertheless he was able to fly 500 miles farther to his home. On alighting from the plane he again became aware of the rapid heart action, inspiratory difficulty, and fluttering sensation. He became nauseated and thirsty but could not retain fluids. He went home and called his family physician who found a very rapid heart rate, administered morphine, and advised admission to an Army hospital.

On the morning of January 29 he was admitted to another general hospital. According to the clinical chart his condition was described as restless and anxious. The pulse rate was 220 a minute, the blood pressure was 70 mm. of mercury systolic and 50 diastolic, the liver edge was palpable 4 cm. below the costal margin, and the temperature was 100° F., orally. The respiratory rate was 24. An electrocardiogram was obtained (figure 1 A, 10:00 a.m., January 29, 1946) and interpreted as showing nodal tachycardia. He was immediately started on quinidine and normal sinus rhythm was present four hours later (figure 1 A, 2:00 p.m., January 29, 1946). Later that evening another paroxysm of tachycardia from a different supraventricular focus appeared (figure 1 A, January 30, 1946) but responded to increased doses of quinidine (figure 1 A, January 31, 1946).

No roentgenogram of the chest was taken. The urine was negative, the sedimentation rate was 21 mm. (Westergren, uncorrected), and the white blood count was 11,500 with 70 per cent neutrophiles, 21 per cent lymphocytes, 5 per cent monocytes, and 4 per cent eosinophiles. For the first day of hospitalization the temperature was 99.4° but fell to normal thereafter. The patient was kept on quinidine until February 17 and was kept at strict bed rest with the accepted "coronary" routine.

When the patient was transferred to this hospital complete physical examination, fluoroscopy, and laboratory studies were done; all findings were entirely normal.

Discussion

On reviewing the records we were first impressed by the rapid evolution of the electrocardiographic changes. These may be noted in the illustrations (figures 1 A, 1 B, and 1 C). On February 19, just 22 days after the initial tracing the record showed only borderline T-waves in Leads I and II as the sole abnormalities (figure 1 C) and six days later the record is entirely normal.

Inspection of the second electrocardiogram taken four hours after the first (figure 1 A, 2:00 p.m., January 29, 1946) reveals normal sinus rhythm, normal QRS complexes and concordant deviation of the S-T segments and T-waves. Electrical systole, the Q-T interval, is slightly prolonged to 0.38 second with

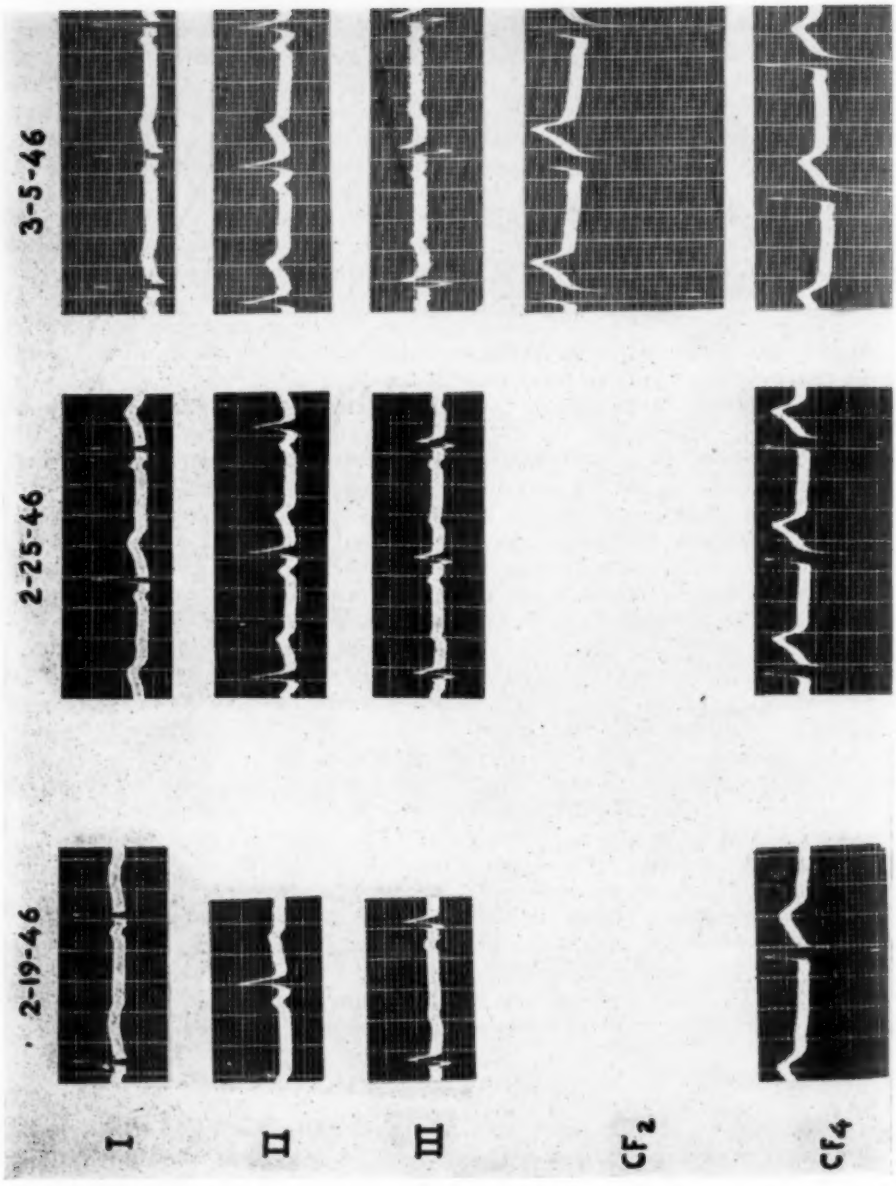

FIG. 1 C. Continuation of previous figures. On February 25, 1946 the tracing is normal. Compare the chest leads from March 11, 1946 with those obtained on February 11, 1946 (figure 1 B). Discussed in text.

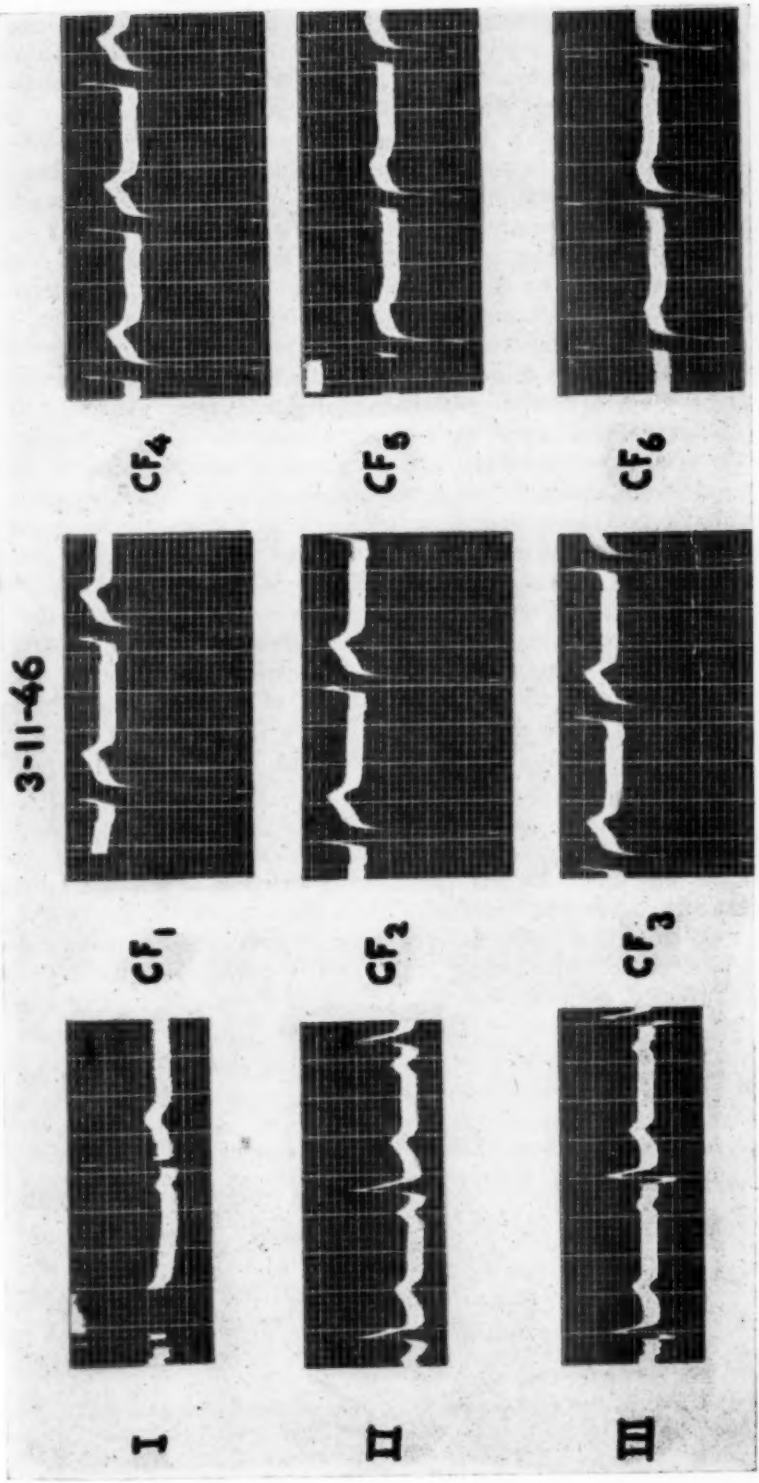

FIG. 1 C (*Continued*).

a normal average at this rate of 0.30 second. This prolongation is due to the widened T-wave. The T-waves are not symmetrical as would be expected in myocardial infarction.

The curve obtained on January 31, 1946 (figure 1 A) shows an electrical systole of 0.52 second while the normal averages 0.34 second. Subsequent records (figures 1 A, 1 B, and 1 C) show a steady rapid return to the normal. In the records available with six chest leads (figure 1 B) the changes are confined entirely to the inverted T-waves. None of the T-waves in the entire series of records shows any of the characteristics of the "coronary type" of T-waves, nor are there any discordant S-T and T deviations. There are no QRS changes of any significance.

A study of the illustrations published by the authors indicated previously will emphasize the points outlined as differentiating these electrocardiographic changes from those due to myocardial infarction. Ward [4] stresses the prolonged Q-T interval that occurs early after the cessation of the paroxysm. This is due to the bizarre, asymmetrical, and prolonged inverted T-wave in each case.

The cause of the changes is not known precisely. Campbell [5] believes that it is a reversible process indicating some degree of exhaustion or strain of the heart muscle. Geiger [1] mentions the long duration of the paroxysm in the case as a possible cause of the exhaustion. Quinidine was also mentioned as a cause, but Zimmerman's [2] cases showed the changes after small doses, and the present case showed the change after only 0.4 gm. of the drug.

Since paroxysmal tachycardia from supraventricular foci occurs most commonly in normal hearts the great importance of differentiating the changes described here from those due to myocardial infarction is self-evident. It is believed that such differentiation can be made readily if attention is paid to the differences described above.

Summary

1. A case of supraventricular paroxysmal tachycardia with prolonged electrocardiographic changes is described.

2. The electrocardiographic differentiation of this condition from myocardial infarction is discussed. Following such cases of paroxysmal tachycardia there appears an inverted, asymmetrical, and prolonged T-wave of bizarre appearance. This causes a prolongation of electrical systole. Further differential points are the concordant S-T and T deviations, the asymmetrical T-waves, and the absence of QRS changes in this condition.

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VOLVULUS OF THE STOMACH *

By LEONARD CARDON, M.D., REGINA S. GREENEBAUM, M.D., and JULIAN ARENDT, M.D., *Chicago, Illinois*

VOLVULUS of the stomach is seldom considered in the diagnosis of acute abdominal disease. Yet it may produce symptoms as sudden and violent as the more familiar volvulus of the intestine. "Volvulus" is defined as abnormal torsion of a portion of the gastrointestinal tract sufficient to produce clinical symptoms.

The earliest reported cases of torsion of the stomach, beginning with Berti's [1] in 1866, were diagnosed only at autopsy. Later a number of surgeons, starting with Berg [2] in 1895, diagnosed the condition clinically and successfully treated it surgically. The roentgenologic appearance of torsion of the stomach has also been described.[3, 4, 5, 6, 7] The medical aspects and especially the clinical diagnosis have thus far received scant attention.

The rare type of acute "complete" volvulus in which the entire stomach participates, was seen in our first case. "Partial" volvulus, the rotation of part of the stomach in relation to the rest of it, was presumed to have occurred in our second patient whose stomach, even when she is asymptomatic, is peculiar in shape, size and position.

CASE REPORTS

Case 1. The sudden onset of severe pain in the left upper abdominal quadrant and repeated vomiting of one hour's duration were the presenting symptoms of a 74 year old male when one of us (L. C.) saw him in consultation with his family physician, Dr. N. S. Sheffner. The pain radiated to the left costovertebral angle and the precordium. A week earlier a similar episode had occurred immediately after the patient had attempted to lift a piano. At that time a physician had made a diagnosis of acute coronary occlusion, administered morphine and advised complete bed rest. The patient remained in bed but was not entirely free from pain during the week between attacks. He had attempted to leave his bed just before the second attack. His past medical history was noteworthy only for an operation for hemorrhoids and rectal prolapse 15 years previously, and for constipation so obstinate that he had taken an enema every day for as long as he could remember.

The patient was writhing, groaning and sweating profusely because of severe pain when he was first seen. The single but strikingly abnormal finding was in the abdomen. The left upper quadrant and lower anterior chest wall were forced anteriorly by a large, palpable, firm, cystic, partially tympanitic, very tender mass.

Acute torsion of the stomach seemed the most likely explanation of this unusual clinical picture. Other diagnoses considered were acute gastric dilatation, incarcerated diaphragmatic or other internal hernia of the stomach, and acute complete pyloric obstruction perhaps superimposed on a chronic obstruction due to a stenosing ulcer or carcinoma.

Aspiration through a stomach tube seemed to be the logical treatment but without further knowledge of the nature of the obstruction it appeared hazardous to attempt it. After a roentgen-ray examination of the abdomen had revealed a high left hemi-diaphragm with a large air bubble above a fluid level in a dilated stomach, a

* Received for publication July 5, 1946.
From the Mt. Sinai Hospital of Chicago.

Levine tube was easily passed. A liter of thin fluid was aspirated and Wangensteen suction instituted. This considerably relieved the patient's pain. Later when drainage had stopped, the mass was still palpable and the patient, while much improved, was still uncomfortable. A large stomach tube was then inserted, a liter of thick, gruelly material aspirated and the stomach washed until the return flow was clear. This gave the patient complete relief from distress and made the tumor disappear. No bile was observed in the gastric contents at any time. The temperature, pulse rate and leukocyte count were normal.

The next day, when the patient was asymptomatic, a barium meal showed the entire stomach rotated through 180° so that the greater curvature was up and the lesser curvature down (figure 1 A). The organ appeared to be rolled together in the shape of a horseshoe. The cardia and pylorus were in such close proximity (figures 1 B and 1 C) that the differentiation of one from the other was difficult. The drawing, figure 1 E, based on the roentgenograms, elucidates the nature of the torsion. The pylorus was elongated and stretched. The esophageal orifice and the fundus with its air bubble were below and medial to the pylorus and duodenal bulb. A small para-esophageal hiatus hernia was found. No other gastric lesion was seen. A loop of colon was interposed between the stomach and the diaphragm. A barium enema revealed a hugely dilated, elongated and redundant colon.

Daily gastric lavage was continued. The patient was discharged on the eighth day of his illness, apparently well, with instructions to use gastric lavage if needed for a recurrence of symptoms.

Five months later another barium meal was administered. The patient had remained entirely free from symptoms in the interim. At this time the roentgen-ray showed an elongated stomach of steer horn shape (figure 1 D) in marked contrast to its previous appearance. The mucosal pattern was also normal. A loop of colon was still interposed between the stomach and the left side of the diaphragm so that the latter was pushed upward and the stomach displaced far medially.

Case 2. The presenting features in the case of this 35 year old woman were the sudden onset of severe upper abdominal pain and repeated vomiting. At first the vomitus contained undigested food and later only gastric juice. Still later non-productive retching occurred repeatedly. The pain was intermittent at the onset but grew progressively more severe with longer paroxysms and less complete relief between paroxysms. The patient writhed and groaned almost continuously at this time. Epigastric tenderness was marked. No rigidity was present. The temperature, pulse rate and leukocyte count remained normal during six hours of increasingly severe symptoms. Heat, cold, nitroglycerine and atropine gave no relief. An obstruction at the pylorus was considered the most likely cause of the attack because of the absence of bile in the vomitus. The pain had begun to subside spontaneously shortly before the administration of morphine and atropine seven hours after the onset of symptoms. Within 12 hours it had disappeared entirely.

Strikingly abnormal mobility of the stomach associated with peculiarity of shape and position was observed on fluoroscopy 10 days after the attack. The organ was

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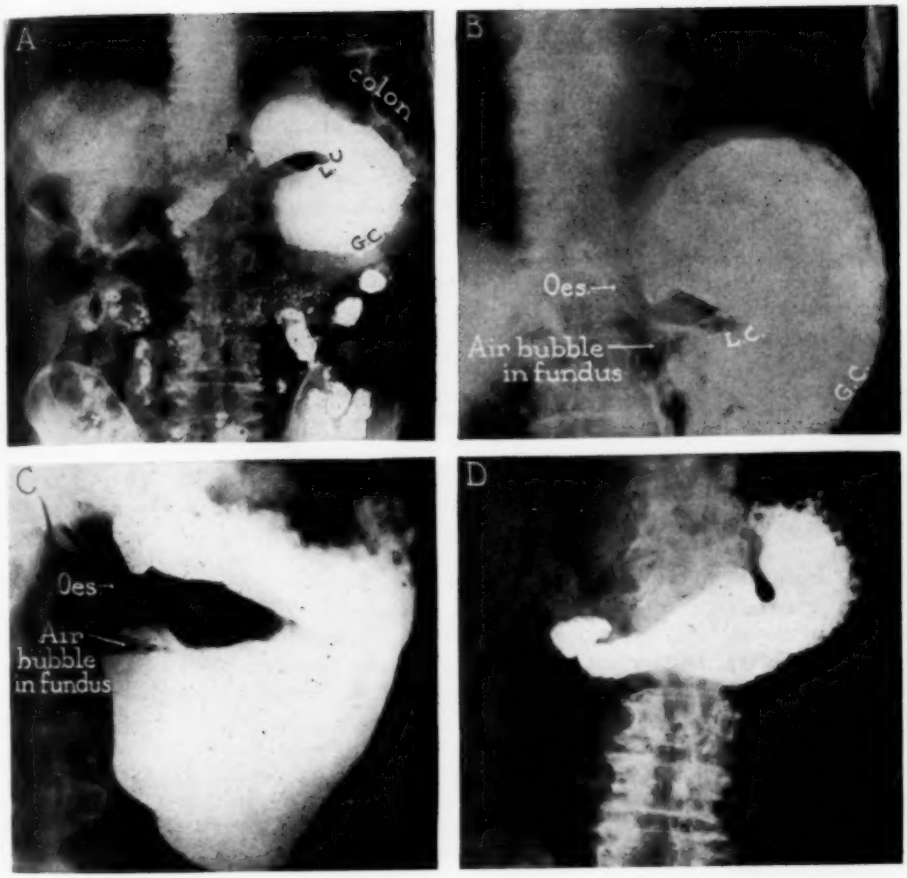
FIG. 1. *Case 1.* A, B and C. Torsion of stomach as it appeared 24 hours after acute attack. Stomach rotated forward and upward 180° about its cardio-pyloric axis. Greater curvature superior; lesser curvature inferior. Cardia below pylorus. Pylorus elongated. In A, loop of colon is interposed between stomach and left hemidiaphragm.

D. Roentgen-ray five months after A, B and C. Normal except that stomach is pushed medially by loop of colon.

E. Drawing of stomach in torsion based on roentgen-rays A, B and C.

F. Diagram. Cardio-pyloric axis of rotation, the usual axis in "complete" volvulus.

P.—Pylorus. G. C.—Greater curvature.
L. C.—Lesser curvature. Oes.—Esophagus.


A
colon
L.C.
G.C.
B
Oes.
Air bubble in fundus
L.C.
G.C.
C
Oes.
Air bubble in fundus
D

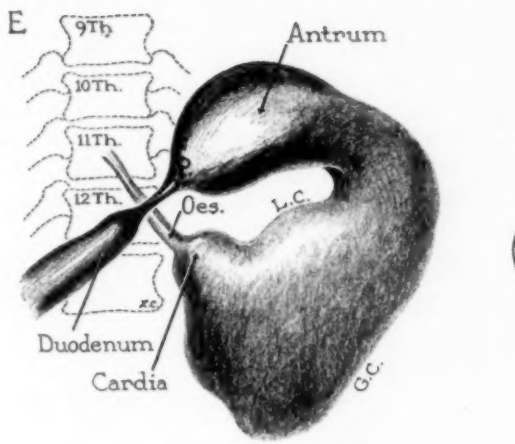

E
9Th.
10Th.
11Th.
12Th.
Antrum
Oes.
L.C.
Duodenum
Cardia
G.C.
F

FIG. 1.

divided into two portions, a hugely distended, air-containing fundus and a smaller, barium-filled corpus and antrum. The distal segment at times rotated upward so that it seemed to "ride" on the distended proximal one (figure 2 B). In this position a fold or kink seemed to be present along the line of junction with the distended fundus. A few minutes later the distal portion dropped to a more normal position (figure 2 A). These motions recurred several times in the course of the fluoroscopic examination. While abnormal movements of the stomach were so obvious to the observer, the patient had no pain. No intrinsic lesion was seen in the stomach or duodenum. Cholecystography was normal. No occult blood was found in the stool. The colon was unusually long with a triple sigmoid loop, splenic flexure high under the diaphragm, transverse colon high in the epigastrium and a redundant hepatic flexure.

Six years after the initial attack the stomach was fluoroscoped again when the patient was symptom free. It had the same shape, position and unusual mobility seen previously (figures 2 C and D) suggesting the permanence of this anatomic abnormality. In the lateral view (figure 2 E) the stomach was shaped like a partially opened jackknife with the concavity directed posteriorly and the convexity anteriorly and superiorly beneath the anterior abdominal wall. The projection of the organ in the sagittal plane occupied a much greater area than normal. The distal and more anteriorly placed chamber of the bilocular organ moved up and down about the proximal and posterior distended fundus. The ease with which a kink could be produced at the juncture of the two segments is evident.

This patient has never had a repetition of the severe pain and vomiting of the initial attack but she does get recurrent episodes of moderate epigastric pain. These usually occur after several days of fleeting, migratory abdominal pain relieved by the passage of flatus. The migratory pain is often associated with fatigue, emotional upsets, or dietary indiscretion. The epigastric pain is much more severe than the migratory pain and is invariably associated with a feeling of enough distention to make the patient wish to remove her corset. Belching never occurs. Antispasmodics sometimes bring relief. If the pain persists, the patient has found that it will disappear if she lies prone across a bed with her trunk hanging vertically, head down, at right angles to her lower extremities.

Comment

Predisposing Conditions. Some or all of the following underlying conditions have been found in reported cases of gastric volvulus.

High Lying, Partially Rotated Stomach. A stomach, partially rotated to a transverse position so that the greater curvature is anterior and the lesser curvature posterior is occasionally seen in a routine gastrointestinal examination (figure 3). This normal variant may predispose to further gastric rotation and volvulus. Such a position may also be acquired, for example, after pneumonectomy which causes displacement and rotation of the abdominal organs to fill in the empty chest cavity.

Fig. 2. *Case 2.* A and B. Ten days after acute attack. Antero-posterior views taken several minutes apart. Note abnormal mobility of corpus about air-distended fundus in bilocular stomach.

L. C.—Lesser curvature.
G. C.—Greater curvature.

C and D. Six years after acute attack. Pictures taken a few minutes apart. Note similarity to A and B.

E. Lateral view, same day as C and D.

F. Diagram showing general direction of rotation in "partial" volvulus. Distal portion of stomach rotates about proximal. Axis of rotation at right angles to long axis of stomach.

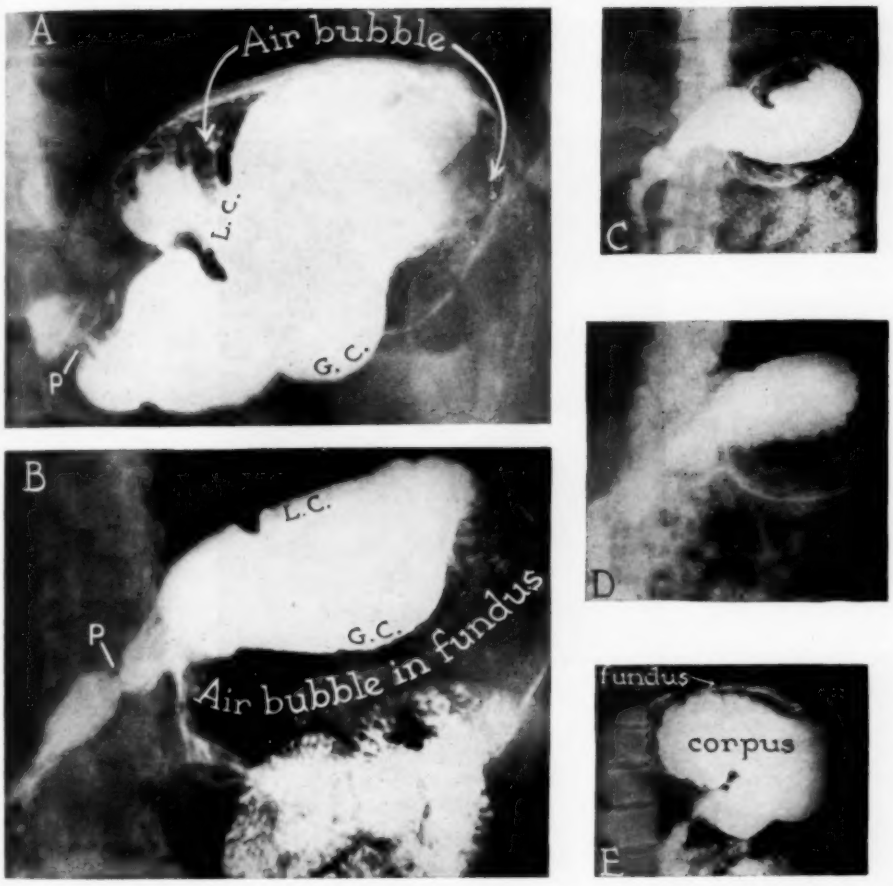

A
Air bubble
L.C.
G.C.
P
B
L.C.
G.C.
P
Air bubble in fundus
C
D
fundus
corpus
E
F

FIG. 2.

Long Gastric Ligaments. Surgeons have found long gastrocolic and gastrohepatic ligaments in patients with spontaneous gastric volvulus.[8, 9] This anatomic peculiarity, congenital or associated with visceroptosis, permits excessive mobility of the stomach. Extensive gastric volvulus would be impossible without abnormally long gastric ligaments.

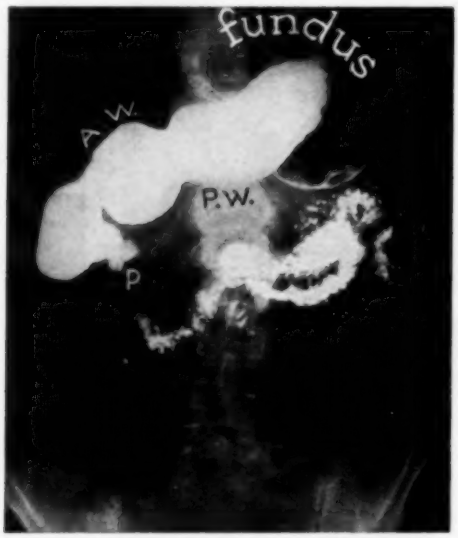


FIG. 3. High lying stomach partially rotated to transverse position. Greater curvature anterior. Lesser curvature posterior. A normal variant.

A. W.—Anterior wall.
P. W.—Posterior wall.
P.—Pylorus.

Redundance of the colon, mentioned in many reports, was conspicuous in our cases. Patient 1 not only had roentgen-ray evidence of redundance, but his severe and persistent constipation was a clinical manifestation of it. Several authors [5, 10] regard gaseous distention in a redundant colon as a cause of rotation of the stomach. Schatzki and Simeone [6] could not produce volvulus of the stomach by experimental distention of the colon with air although the stomach was displaced upward by this procedure.

Interposition of a loop of colon between the stomach and the leaf of the diaphragm has been observed in patients with gastric volvulus.[4, 11] This may be a causative or a coincidental circumstance. Gaseous distention of such an interposed colonic loop may produce the initial displacing force that leads to gastric torsion.

Diaphragmatic Hernia. The displacement and rotation of the stomach produced in diaphragmatic herniation or eventration is another possible cause of gastric volvulus. The small paraesophageal hiatus hernia probably played no etiological rôle in our first case.

Vigorous peristalsis immediately after antiperistalsis has been postulated as another means of initiating gastric volvulus.[12, 13]

Sudden Rise in Intra-abdominal Pressure. The acute onset of the catastrophic symptoms in case 1 immediately after an attempt to lift a piano suggests a rise in intra-abdominal pressure as a precipitating cause of the volvulus.

Combination of Predisposing Conditions. The stage setting for impending volvulus of the stomach in the first case may be visualized as follows: The abdominal cavity is crowded by a dilated, redundant, over-filled colon. The entire gastrointestinal tract, including the stomach, is abnormally mobile because of congenitally long mesenteries and intra-abdominal ligaments. A loop of colon is interposed between the stomach and the left hemidiaphragm. Sudden exertion with contraction of the muscles of the abdominal wall and the diaphragm causes an abrupt diminution of intra-abdominal volume. This forces the loops and coils of the stomach and bowel to rearrange themselves within a smaller space. The stomach with its greater possible range of motion because of its abnormally long ligaments may be caught at the moment of compression in such a situation (e.g. high lying transverse position) that further rotation is easier than return to the normal position. Once it is forced beyond this critical position, the persisting pressure of the abdominal and diaphragmatic muscles acting directly on the stomach or indirectly through the interposed intestinal loops, forces it to continue its abnormal rotation to the point at which symptoms occur. After the torsion is produced, the abnormal length of the ligaments may prevent them from exerting enough tension to reduce the volvulus even after the intra-abdominal pressure is lessened. The hyperdistention of the stomach which rapidly ensues tends to hold it so tightly wedged between the surrounding organs that at operation in other similar cases it has often been found impossible to untwist or manipulate the stomach until its contents have been removed through a trocar.

Our first patient must have had suddenly increased intra-abdominal pressure many times previously in his 74 years of life, without developing gastric volvulus. When he had the acute attack either the rise in intra-abdominal pressure was greater, or the stomach was in the critical position favorable for torsion at the moment of exertion, or both may have occurred simultaneously.

Explanation of Symptoms. Whether or not rotation of the stomach produces symptoms depends upon the extent of disturbance in its peristaltic movements, secretion, and circulation. The tremendous gastric distention found in cases of volvulus is a consequence both of the inability of the stomach contents to escape because of the torsion and of the hypersecretion of fluid and the transudation of serum resulting from the disturbed circulation. These mechanisms explain the patients' pain as well as the enormous amount of fluid in the stomach. Maximum gastric hyperdistention in case 1 must have been far greater than the films (figures 1 B and C) show, since these were taken after more than two liters of fluid had been removed.

The repeated emesis without bile in the vomitus, followed later by nonproductive retching in case 2, was probably the result of twisting of the stomach to such a degree that it became divided into two disconnected compartments. The proximal compartment remained connected with and open to the esophagus, but was separated from the distal chamber so that bile, even if it entered the stomach through the pylorus, could not pass the obstruction between the chambers and hence could not reach the esophagus. After the proximal compart-

ment had been emptied by repeated emesis, further attempts at vomiting resulted only in non-productive retching. In case 1, the degree of twisting was sufficient to explain the inability of bile to reach the esophagus.

Types of Volvulus. Total. When the entire stomach rotates upon itself, as in case 1, the condition is known as "total" volvulus. The stomach may twist as much as 360 degrees. In our case it must have been twisted to a greater degree at the height of the pain than the 180 degrees observed in the roentgen-ray examination 24 hours later when the patient was asymptomatic.

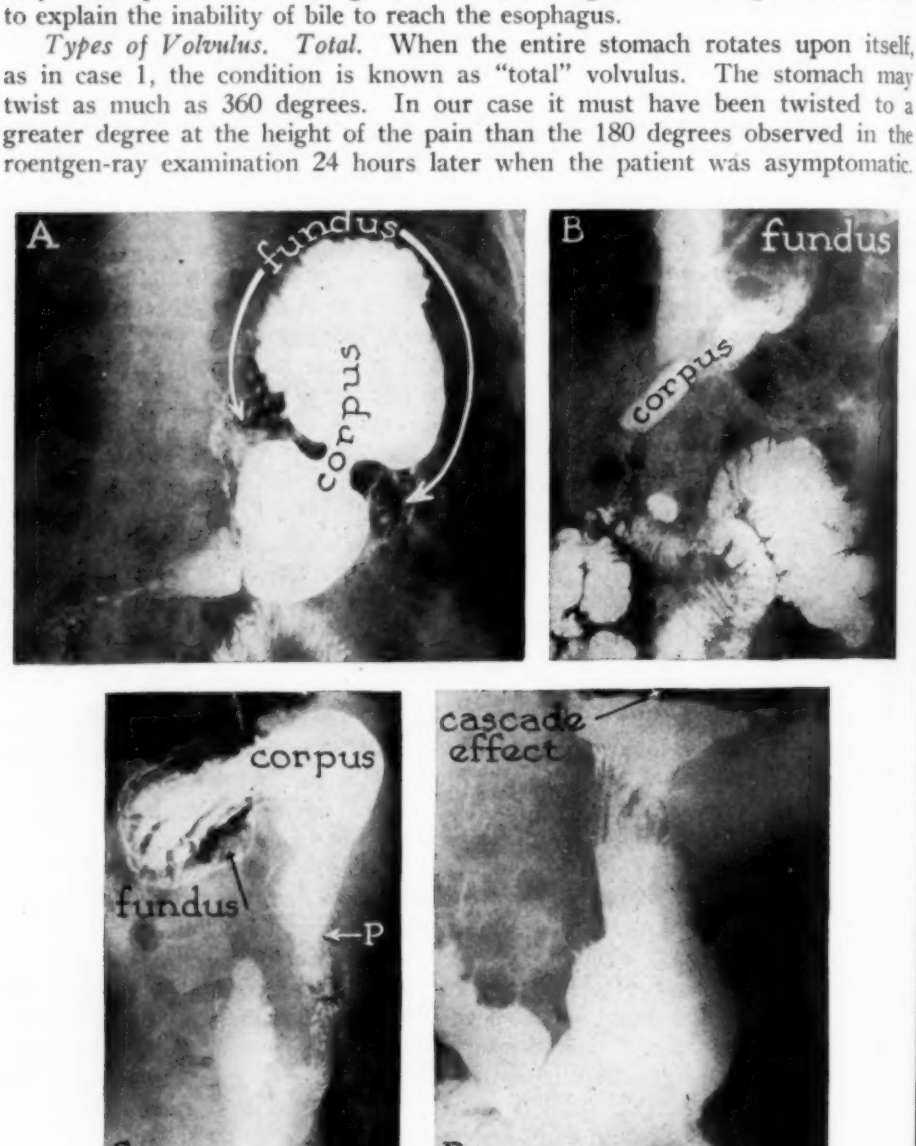


FIG. 4. Bilocular stomach of patient who complained only of left upper quadrant pain and belching of many years' duration. Not in volvulus.

A. Two chambers.

B. Small corpus extending from large, air-containing fundus, like a finger from an air-distended rubber glove.

C. Lateral view. Corpus makes sharp knee bend with fundus.

P.—Pylorus.

D. "Cascade" produced by fold in redundant stomach.

The degree to which the stomach can be rotated without the production of clinical symptoms is noteworthy (figures 1 A, B and C).

Partial volvulus occurs when one portion of the stomach twists on another portion, as in case 2. Twisting of this type may occur if the mid-portion of the stomach is indurated or fixed by intrinsic or extrinsic lesions such as ulcer, carcinoma, hour glass stomach, adhesions or herniation through the omentum. None of these conditions was present in this case. Instead, the bilocular shape and peculiar position of the organ presumably predisposed it to abnormal rotation. The shape and position of the stomach are not unique. Figures 4 and 5 illustrate a similar gastric condition in two other patients who had no symptoms of volvulus. Their complaint was abnormal gaseous distention of the sort found in habitual aerophagia.

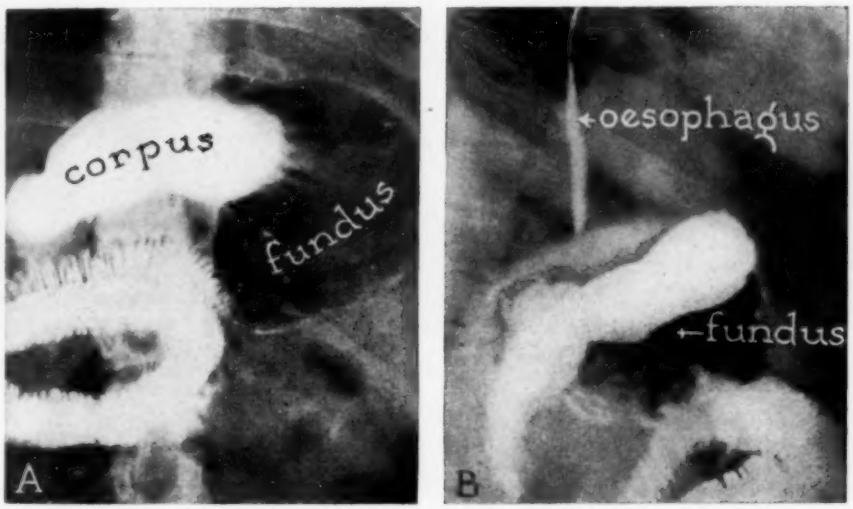


FIG. 5. Stomach similar to figures 2 and 4. Patient's only complaints were precordial pain and belching.

A. Antero-posterior.
B. Lateral.

Figure 6, the artist's conception of a lateral view of this type of stomach based on the roentgenograms in figures 2, 4 and 5, clarifies its characteristic features. The esophagus passes into a hugely distended, balloon-like fundus that lies against the posterior abdominal wall beneath the left hemidiaphragm just to the left of the spine. The entire stomach is shaped like a partially opened jackknife with its concavity posterior and to the right and its convexity just beneath the abdominal wall, anterior, superior and to the left. The upper, more or less horizontal limb of the jackknife is made up of the hyperdistended fundus from which the first portion of the corpus extends anteriorly to the abdominal wall. The corpus is much smaller than the fundus and may arise directly from it like a finger from the palm of an air-distended rubber glove (figure 4 B) or may be separated from it by a constricted portion of the stomach of some length. The lower limb of the jackknife composed of the rest of the

corpus and the pylorus, bends back more or less sharply on the upper limb at the anterior convexity or "knee." It extends posteriorly, to the right and inferiorly. The distention itself may displace the fundus downward and posteriorly to produce the jackknife shape here described. The fundus may be further depressed by a loop of colon between it and the diaphragm so that the anterior bend may actually be the most superior portion of the stomach (figure 4 C). The organ may be larger and more redundant than normal. The cascade effect in figure 4 D was produced by a fold in a redundant stomach. Abnormal mobility of the distal limb about the proximal one in an up and down, and

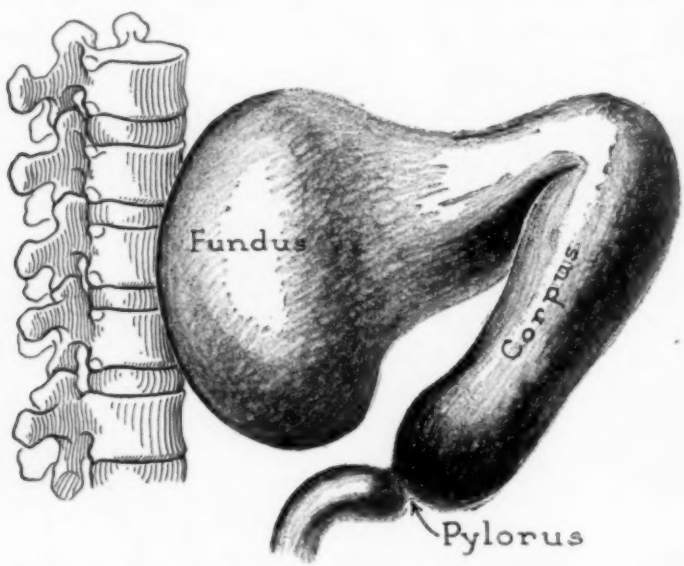


FIG. 6. Drawing of "jackknife" type of stomach based on roentgen-rays in figures 2, 4 and 5. Lateral view. Large, air-distended fundus posterior. Convexity anterior and superior. Horizontal, superior limb continuous with distended fundus.

perhaps also in a rotatory direction, was seen in these cases. To emphasize the the abnormality of these stomachs, anteroposterior and lateral views of the normal organ are inserted for camparison (figure 7).

The peculiar shape and position of this type of stomach may be a congenital anatomic variation, or the hyperdistended, air-filled fundus may be a manifestation of air swallowing, although this was not observed in our patients. In infants, overdistention of the fundus is seen more often in the breast or bottle-fed, who inevitably swallow air, than in the spoon-fed.[14]

Axis of Rotation. The stomach in case 1 rotated above the cardio-pyloric axis (figure 1 F). "Complete" volvulus and severe obstruction are more likely to occur in rotations about this axis. A case with roentgenograms of a stomach similar in direction of rotation, completeness of involvement and position in volvulus was reported by Caillods and Cottet.[7]

The axis in case 2 was perpendicular to a line joining the cardia and pylorus (figure 2 F). This axis is more common in "partial" volvulus in which only a part of the stomach revolves about the remainder.

Diagnosis. The sudden onset of excruciating pain high in the abdomen, especially in its left upper quadrant, with or without a visible and palpable mass, and repeated emesis without bile in the gastric contents followed by non-productive retching, should suggest the possibility of volvulus of the stomach. A history of immediately preceding sudden increase in intra-abdominal pressure, absence of peritoneal irritation and normality of the temperature, pulse rate and leukocyte count would tend to confirm the diagnosis. In some cases where a fold is produced near the cardia by the torsion, it may be impossible to pass a stomach tube. This may be of diagnostic value.

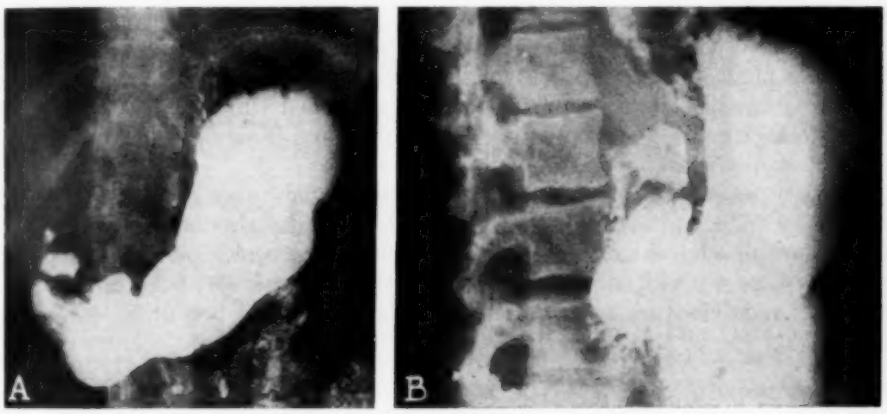


FIG. 7. Normal stomach.
A. Antero-posterior.
B. Lateral.

Something in the clinical picture of our first case almost instinctively suggested the diagnosis. Berg [2] had the same feeling about his case, as indicated in the following translation from his report: "A sound was passed 47½ cm. from the teeth and here met with definite obstruction. . . . That we were dealing with a case of obstruction to the passage of food into the stomach was clear . . . and we could explain the peculiar stormy course of the illness, the stomach-like shape and location of the tumor and the obstruction to the passage of the stomach tube in no other way than by the assumption of an acute volvulus of the stomach."

The diagnosis was made in retrospect in our second case and must remain presumptive. No roentgen-ray examination was made during the acute attack. Ten days later, when abnormal mobility of a portion of the stomach was seen, no actual volvulus was present. In the absence of other gastrointestinal abnormalities and with the known unusual mobility of the distal portion of the stomach, the clinical picture of the acute attack can best be explained by assuming that the distal portion of the stomach twisted on the proximal to a sufficient degree to produce obstruction.

Treatment. Prophylactic. A patient who has previously had volvulus of the stomach or one whose stomach is high lying and partially rotated should avoid strain that may produce sudden, marked increase in intra-abdominal pres-

sure. Overdistention of the colon should be prevented because it might precipitate gastric torsion. A daily bowel evacuation, avoidance of gas forming foods, antispasmodics and mild sedatives may accomplish this. Large meals with their consequent overdistention of the stomach should be avoided. If gastric lavage was previously effective in the treatment of an acute attack, the patient should be taught its technic and should be urged to use it early in case of recurrence.

Active. The essence of the active treatment of gastric volvulus is decompression of the stomach by medical or surgical means. The first step should be an attempt at gastric aspiration and lavage. If successful, removal of the stomach contents may permit that organ to untwist itself. This is in contradistinction to a widely prevailing idea that immediate surgery is always indicated to avoid a fatal outcome. Since volvulus may produce an obstruction near the cardia, passage of a stomach tube should be performed with the greatest caution. If the stomach cannot be emptied by this method and if signs of obstruction and strangulation increase, operation is imperative.

In patients with partial volvulus, antispasmodics may stop mild attacks, perhaps by reduction of the strong peristalsis that may produce a kink between the portions of a bilocular "jackknife" stomach. If an attack persists, the patient should assume a position in which the trunk hangs vertically, head down. This maneuver is advised on an empirical basis because of its benefit to our second patient.

Summary

Two cases of volvulus of the stomach with recovery without surgery are reported.

Acute "complete" gastric volvulus occurred in the first case. The probable underlying anatomic peculiarities associated with this condition are: a high-lying, partially rotated stomach, long gastric ligaments, redundance of the colon and interposition of a loop of colon between the stomach and the left hemidiaphragm.

The significance of a marked increase in intra-abdominal pressure following sudden effort is stressed as a precipitating factor in this disease.

Acute "partial" gastric volvulus presumably occurred in the second patient whose stomach has a characteristic anatomic variation in shape and position which we have named "jackknife" stomach.

The outstanding diagnostic features of our cases were: severe pain high in the epigastrium or left upper abdominal quadrant, repeated vomiting without bile in the vomitus (followed by non-productive retching in our second case) and absence of evidence of inflammation. The combination of these phenomena with a history of sudden, marked, straining effort, and the rapid appearance of a left upper quadrant mass, tender and cystic, pushing the left costal arch anteriorly, suggested the clinical diagnosis in our first case.

A stomach in volvulus, even with severe symptoms, may spontaneously untwist itself.

The essence of the active treatment of gastric volvulus is decompression of the stomach by medical or surgical means.

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PERITONITIS COMPLICATING A CASE OF NEPHROSIS: TREATMENT WITH PENICILLIN INTRAPERITONEALLY *

By Louis Levy II, M.D., *New Orleans, Louisiana*

Case Report

J. G., white male, aged 12 years, was admitted on December 10, 1944 with a chief complaint of generalized swelling. Nine days previously the patient had developed a "cold" which continued for one week and was accompanied by a low grade fever and general malaise. The patient then noticed a progressive swelling beginning first in the eyelids, and later involving the ankles, legs, hands, and abdomen. The rest of his history was noncontributory.

Physical examination on admission revealed temperature of 99° F., respirations 30, pulse 120, and blood pressure 120 mm. of mercury systolic and 70 mm. diastolic. The only pertinent point on physical examination was anasarca, with four plus pitting edema of the lower extremity, ascites, and marked facial edema. Ophthalmoscopic, cardiac, and pulmonary examinations revealed no abnormalities.

Laboratory examinations on this admission revealed the following: Daily urinalyses showed specific gravity varying from 1.009 to 1.024, 3 to 4 plus albumin, and occa-

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From the Department of Medicine, Louisiana State University School of Medicine, and the Charity Hospital of Louisiana at New Orleans.

sional hyaline and fine granular casts. Red blood cells were never found. Repeated blood counts revealed red blood cells varying from 4.5 to 4.9 million; hemoglobin varying from 12.5 gm. to 15.5 gm.; white blood cells varying from 12,500 to 15,950, with 74 to 79 per cent polynuclears, 1 to 4 per cent eosinophiles, 2 to 5 per cent monocytes, and 15 to 20 per cent lymphocytes. Urea nitrogen varied from 10 to 13.1 mg. per cent, cholesterol from 454 to 555 mg. per cent, serum protein from 4.5 to 5.79 gm. per cent (A/G ratio of 1 to 1). Blood Kline and Kolmer tests were negative. The phenolsulphonephthalein test showed 70 per cent excreted in the first hour and 15 per cent in the second hour. A roentgenogram of the chest was reported as showing a normal configuration of the cardiac shadow. Intravenous pyelograms showed the kidney shadows to be normal in size, shape, and position. Pelvis, calices, ureters, and bladder appeared to fill in a normal manner. An electrocardiogram was within normal limits. Complete dental roentgen-rays were negative.

On the basis of a negative past history for kidney disease, absence of hypertension, presence of anasarca, repeated findings of four plus albumin on urinalysis without red cells, evidence of good renal function, lowered serum protein with lowered A/G ratio, the patient was considered to be either a case of nephrosis or the nephrotic stage of glomerulonephritis. The treatment consisted of repeated blood and plasma transfusions, amino acids given orally and intravenously, low salt diet, and the use of diuretics. Edema decreased somewhat, and the general condition remained good. He was discharged to the out-patient clinic on February 16, 1945.

The patient was readmitted on March 24, 1945 because of increasing edema. The findings on this admission revealed no essential changes from those found on the previous admission with the exception of an increase in the degree of anasarca. The blood pressure was 118 mm. of mercury systolic and 65 mm. diastolic. Urinalysis showed the same findings as previously except that in one specimen eight red blood cells per high power field were found. The blood count remained the same. Urea N remained below 16 mg. per cent. Serum proteins varied between 3 and 4.5 gm. per cent, and the A/G ratio was 1/1.7. The phenolsulphonephthalein test showed 50 per cent excreted in the first hour and 15 per cent in the second hour.

On treatment similar to that given on the previous admission, the patient remained afebrile, and improved. On April 29, 1945 his temperature rose to 104° F., and he developed severe generalized abdominal pains accompanied by nausea and vomiting. There was no diarrhea. An increase in the degree of abdominal distention was noted with a tympanitic note on percussion around the umbilical region. There was exquisite generalized abdominal tenderness and rebound tenderness. Physical examination of the chest and a roentgenogram were negative at this time. Urinalysis was the same as previously. The patient developed the typical picture of an acute severe generalized peritonitis. A diagnosis of peritonitis complicating nephrosis was made and a paracentesis was performed yielding 4000 c.c. of white turbid flow which showed gram positive diplococci on smear. A diagnosis of a pneumococcal peritonitis was considered most probable and 100,000 units of penicillin in 100 c.c. of normal saline were injected into the abdominal cavity along with the continuous use of 20,000 units of penicillin intramuscularly every two hours. On the next day, following removal of 500 c.c. of turbid fluid, 100,000 units of penicillin in 200 c.c. of normal saline were introduced into the peritoneal cavity. The patient's general condition showed a marked improvement, his temperature dropped to 100° F., and his abdominal symptoms were diminished in severity. During the next three days repeated paracenteses were performed with instillation of 40,000 units intraperitoneally each time. Repeated cultures of the fluid were negative. The peritoneal fluid became less turbid, the patient's abdominal symptoms completely disappeared, and he became afebrile. Repeated blood cultures, blood agglutinations, stool cultures and examinations were negative during and following this febrile period.

Following this episode the patient's anasarca began to subside. He received the same treatment given on his first admission and was given 100 gm. of Essenamine * daily by mouth. His weight dropped from 94 lbs. to 79 lbs., and most of his edema subsided. Urinary abnormalities disappeared except for a trace of albumin. Repeated quantitative urinary albumin determinations performed prior to his peritonitis had shown as much as 121.8 gm. of moist albumin in 24 hrs. After his attack of peritonitis subsided the excretion fell to 4 gm. in 24 hrs.

On June 23, 1945 he was discharged to the out-patient clinic. At that time his weight was 87 lbs., and his urine showed a trace of albumin. He has been followed in the clinic over the past seven and a half months, and although his general condition has remained the same and his weight has only increased to 98 lbs., his urinary albumin has again become four plus, and his serum proteins are 3.37 gm. per cent with an A/G ratio of 1/1.2. Blood urea N has remained below 10 mg. per cent, and the phenolsulphonephthalein excretion has varied between 65 and 75 per cent.

Comment

A case of lipoid nephrosis (or the nephrotic stage of glomerulonephritis) complicated by pneumococcal peritonitis is presented. The peritonitis cleared rapidly under therapy with penicillin intraperitoneally and intramuscularly.

We realize that spontaneous recovery from pneumococcal peritonitis in cases of nephrosis is not uncommon. The severity of this patient's symptomatology with the early response to therapy leads us to believe that the course of his illness was definitely beneficially altered by administration of penicillin.

HEMOLYTIC ANEMIA COMPLICATING PRIMARY ATYPICAL PNEUMONIA WITH COLD ISOHEMAGGLUTININS †

By Biagio Battaglia, *Brooklyn, N. Y.*

Hemolytic anemia of varying severity, associated with cold isohemagglutinins, in primary atypical pneumonia has been previously reported.[1, 2, 3] In a series of 200 cases, hemolytic anemia was noted in 11.[2] It occurred at a time when the maximal titer of cold agglutinins is most often encountered, between the middle of the second and the middle of the fourth week. The presence of cold agglutinins in high titer does not necessarily result in such hemolytic phenomena.[3] In some of the previously reported cases the administration of a sulfonamide compound has been considered a contributory cause of the hemolytic crisis.[1]

The following case history is being reported because a severe hemolytic crisis, associated with a high titer and high thermal activity of cold agglutinins, occurred during an episode of primary atypical pneumonia. Cold isohemagglutinins were still demonstrable in the patient's blood in high titer two months following the acute hemolytic crisis. No sulfonamide compound was administered during her illness. A transfusion of blood was complicated by the presence of Rh antibodies.

* A hydrolysate of lactalbumin, supplied us by Frederick Stearns & Co.

† Received for publication March 6, 1947.

Case Report

Mrs. N. G., a 68 year old mother of five children, was admitted to the hospital on December 13, 1946. The patient was a known diabetic under my private care since 1937. Two weeks prior to admission, she developed an unproductive cough. One week later, physical examination revealed signs of a severe bronchitis throughout the chest. She was afebrile and her color appeared to be good. A mixture of codeine, ephedrine and Stokes expectorant, in addition to 10 drops t.i.d. of a saturated solution of potassium iodide, was prescribed. The next day, the patient and her family noted for the first time that her urine was dark red. This discoloration persisted for a few days. The cough became more severe. The patient was reëxamined three days prior to her admission to the hospital. At that time, she appeared unusually pale; wheezy respiratory sounds were most pronounced over the right upper lobe; the rectal temperature was 100.5°. A urine specimen appeared orange in color but was otherwise not remarkable. Penicillin solution intramuscularly was administered every three hours for three days prior to hospitalization.

On admission to the hospital, the patient appeared paler, weaker and more dyspneic than she had previously been. She coughed continuously and raised very little sputum. Her temperature was 99, pulse 90, blood pressure 170 mm. Hg systolic and 80 mm. diastolic. Sibilant râles were audible in the right upper lobe and, to a less extent, in the remaining lung fields. The heart sounds were normal. The abdomen was slightly distended. The liver and spleen were not palpable. Rectal examination revealed dark brown feces. A roentgenogram of the chest revealed normal lung fields. Penicillin therapy was continued and elixir terpene hydrate with codeine was substituted for her previous cough medications.

Laboratory examinations of the blood on the morning following admission to the hospital revealed: 6.9 gm. or 43 per cent hemoglobin; 29,000 white blood cells with a differential of 52 per cent polymorphonuclears, 38 per cent lymphocytes, 9 per cent monocytes, 1 per cent eosinophiles, and 32 nucleated red blood cells per 100 white blood cells. The red blood cells were polychromatophilic and varied in size and shape; a red blood cell count was not done because the blood clotted in the pipette immediately after it was drawn. For the same reason a number of smears had to be pulled before a satisfactory one was obtained. The urine examination revealed a specific gravity of 1.020, no albumin, 1 plus sugar, no acetone and an occasional white blood cell.

Following the report of these laboratory findings, it became apparent that the patient was suffering from a hemolytic crisis associated with cold isohemagglutinins. The next day, December 15, 1946, her condition appeared worse. The blood hemoglobin was reported as 5.7 gm. Reticulocytes in a blood smear were 15 per cent of the red blood cells. The patient's blood group was O. A urine examination revealed the presence of urobilinogen to a dilution of 1 : 50, a negative benzidine test for occult blood, and the absence of bile. That evening, blood was withdrawn for the estimation of the cold agglutinin titer, blood fragility, icterus index, and Rh grouping. A warm syringe was used to prevent immediate clotting of the blood. One thousand c.c. of Rh positive whole blood from a blood bank was cross matched with the patient's blood, and then slowly transfused into the patient. Precautions were taken to keep the blood warm. No untoward reaction occurred during the transfusion. The next morning the patient appeared to be definitely improved.

The laboratory reported cold agglutinins to be present to a dilution of 1 : 2048 at icebox and room temperatures, and absent at incubator temperatures. Determination of the fragility of the red blood cells revealed beginning hemolysis at a NaCl concentration of .48 per cent, and complete hemolysis at .36 per cent. The icterus index was 20.7 units, and bilirubin determination .55 mg. per cent at 15 minutes. The patient's blood was Rh-negative.

On the afternoon of following day, December 16, 1946, the patient's temperature rose for the first time from 100 to 102° F. It remained elevated for another 24 hours, then began to fall by lysis and remained below 100° from December 19 until she was discharged to her home on December 29. During the height of her febrile reaction, she developed clinical jaundice for a few days; the physical signs in the chest increased; slight cyanosis appeared and required nasal oxygen; penicillin was discontinued and streptomycin was administered in a dosage of 1600 mg. daily from December 17 to December 21. After the acute febrile reaction subsided, her general condition improved. On the day she was discharged from the hospital, she was still very pale; physical signs were still present in the chest.

In addition to the treatment noted, she received 15 units of a concentrated liver extract intramuscularly daily, ferrous sulfate and multiple vitamin capsules. The diabetes was controlled with insulin.

Laboratory examination following the transfusion of blood revealed: on December 16, 8 gm. or 53 per cent hemoglobin, 13,300 white blood cells, with a differential of 63 per cent polymorphonuclear cells, 23 per cent lymphocytes, 6 per cent monocytes, 6 per cent eosinophiles, 2 per cent basophiles; on December 18, 7.2 gm. or 46 per cent hemoglobin; and on December 26, 47 per cent hemoglobin and 2,200,000 red blood cells. Urine examinations were performed daily for three days following the transfusion. A benzidine test for occult blood was consistently negative. The presence of bile in the urine was reported for the first time on December 19.

Following the patient's discharge to her home, 10 mg. daily of folic acid was substituted for the liver extract. On February 17, 1947, she appeared to be in excellent health. The lungs were clear. Fluoroscopic examination of the chest was negative. Her blood hemoglobin was 14 gm. (Sahli), and a blood smear was normal. A blood cold isohemagglutinin determination was positive to a dilution of 1:512 at 5° C., and negative at a room temperature of 20° C.

An Rh factor determination of her husband's blood was reported as positive. A review of the patient's past pregnancies revealed that she had given birth to seven living children. The second and fourth children both died when 22 days old of "blood poisoning." She spontaneously aborted a two months pregnancy, two years before her youngest living child, aged 23 years, was born. She had never received a transfusion of blood prior to her recent illness.

Summary

1. A case of hemolytic anemia complicating primary atypical pneumonia, associated with cold isohemagglutinins of high titer and high thermal activity is reported.

2. The cold isohemagglutinins were still demonstrable in the patient's blood two months after the acute hemolytic crisis. They were present in a dilution of 1:515 at 5° C., though absent at temperature of 20° C., at this time.

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1. Dameshek, W.: Cold hemagglutinins in acute hemolytic reactions, Jr. Am. Med. Assoc., 1943, cxxiii, 77–80.

2. Finland, Maxwell, et al.: Cold isohemagglutinins in primary atypical pneumonia, Jr. Clin. Invest., 1945, xxiv, 458–473.

3. Young, L. E.: Clinical significance of cold hemagglutinins, Am. Jr. Med. Sci., 1946, ccxi, 23–39.

EDITORIAL

NOTES ON THE PROBLEM OF BLEEDING PEPTIC ULCER

THOUGH it is not possible to determine the mortality rate from hemorrhage in peptic ulcer, available statistics are sufficient to prove that the condition is frequently fatal. Moreover there is no evidence that the percentage of fatalities has decreased in the last two decades.

There are a number of difficulties in arriving at a dependable mortality rate from the literature. The standards for *diagnosis* of peptic ulcer vary in different series reported. Practically all series deal only with patients admitted to hospital, thus omitting many instances of minor hemorrhage treated in the home, and no doubt a few of sudden death outside the hospital due to fulminating hemorrhage. Certain papers deal only with cases of severe or massive hemorrhage. In many reports hemorrhage from peptic ulcer is dealt with merely as a subdivision of the general subject of hematemesis, thus omitting those cases in which melena is the only manifestation of the bleeding. Certain series are compiled exclusively from cases which have been treated by one type of regime, those admitted in a terminal state not being included. Some authors draw distinctions between the death rate due to the hemorrhage alone and that due to such complications as perforation or myocardial damage. It is not surprising then that reported mortality rates vary from zero to 50 per cent, with the larger and more inclusive groups usually showing 4 to 10 per cent fatalities.

Such variations in criteria, together with the relatively small number of cases in many reported series, probably account in larger measure for the incongruity of published statistics on the mortality of bleeding ulcer than do the variations in the methods of treatment in the reporting institutions. This point of view is supported by consideration of the many factors which may influence survival or death in bleeding from the ulcerations of the stomach and duodenum which are grouped clinically as peptic ulcers. Certain of these factors are not only variable in occurrence but also little influenced by dietetic regimes or modes of supportive therapy.

Though the literature contains relatively few analyses of the causes of death in bleeding peptic ulcer enough data are available to indicate that these are divisible into three classes: (1) the rapidity and volume of the hemorrhage; (2) complications occurring coincidentally with or as a consequence of the hemorrhage; (3) the presence of other disease conditions in the patient which play a part in determining the outcome.

There is no question but what loss of blood is the cause of death in the majority of fatalities associated with the condition under discussion; though it by no means accounts for all deaths. Various authors have studied separately the cases showing evidence of massive hemorrhage and all concur in

the higher mortality in this group. In Heuer's [1] clinic 161 cases were classified as severe or massive hemorrhage from peptic ulcer and in this group a mortality of 13 per cent occurred. Bohrer [2] collected, from hospital statistics and from a questionnaire to leading surgeons, data on 1556 cases of massive hemorrhage showing a mortality rate of 17 per cent. Chiesman,[3] in reviewing 191 cases of severe hemorrhage from peptic ulcer, found that 25 per cent had died. Bennett and his associates [4] in a series of 122 cases in which the alterations in total blood volume were followed during hemorrhage, found that the deaths that occurred were confined to the group showing the most severe diminution in blood volume. Similar data indicating the major rôle of blood loss in causing fatalities have been published by Allen and Benedict,[5] Rafsky and Weingarten [6] and others.

While it is not difficult in retrospective analysis to demonstrate that severe hemorrhage carries statistically a greater risk of death than moderate bleeding, it is difficult to draw valuable therapeutic deductions from this knowledge at the bedside. The clinical course of bleeding in such patients is extremely varied. Occasionally bleeding from peptic ulcer is fulminant from the onset and the patient dies in collapse within a few hours.[7] On the other hand the initial bleeding may be mild but a rapidly fatal recurrence may appear several days later. Quite rarely there is an apparently continuous slow bleeding with death after a week or more. The type however, most commonly seen in fatal cases consists of recurrent severe hemorrhages over a period of a number of days, each signalized by vomiting of blood and often by simultaneous passage of bloody stools, accompanied by profound drop in blood pressure, dyspnea, restlessness, apprehension and other evidences of shock.

Acquaintanceship with these various types of fatal bleeding does not assist greatly in predicting a fatal outcome in the individual case, for entirely similar clinical symptoms and laboratory evidences of severe blood loss are seen in cases which, though obviously in great danger, yet stop bleeding and recover. In fact statistics of massive hemorrhage indicate that at least four out of five recover.

It is true that abundant statistical evidence exists that death as a result of loss of blood in these cases of peptic ulcer is far more apt to occur in patients over 40 years of age than in the younger age group but since it does

[1] Heuer, G. J.: The treatment of peptic ulcer, 1944, J. B. Lippincott Co., Philadelphia.
[2] Bohrer, J. V.: Massive gastric hemorrhage, Ann. Surg., 1941, cxiv, 510.
[3] Chiesman, W. E.: Mortality of severe hemorrhage from peptic ulcer, Lancet, 1932, cxxiii, 722.
[4] Bennett, T. I., Dow, J., *See* Sanders, F. P., and Wright, S.: Severe hemorrhage from the stomach and duodenum, Lancet, 1938, ii, 651.
[5] Allen, A. W., and Benedict, E. B.: Acute massive hemorrhage from duodenal ulcer, Ann. Surg., 1933, xcviii, 736.
[6] Rafsky, H. A., and Weingarten, M.: Bleeding peptic ulcer, Jr. Am. Med. Assoc., 1942, cxviii, 5.
[7] Hinton, J. W.: Fatal hemorrhage in peptic ulcer treated conservatively, Am. Jr. Surg., 1933, xxii, 315.

occur at any age, there is no security to be felt in the case of a younger individual.[2, 6, 8, 9]

The postmortem examination of cases of peptic ulcer that have died of hemorrhage usually shows a chronic ulcer of the lesser curvature of the stomach or of the posterior wall of the duodenum with, in its fibrous base, a wide open artery. However, the ulcer may be acute rather than chronic or be a mere erosion difficult to detect without careful search. The pathological lesions in the cases of massive hemorrhage which recover spontaneously are less well known. Later roentgenological studies after recovery may indicate the site of the ulcer, but in a considerable percentage of cases yield entirely negative findings.

The importance in therapeutic management of combating the effects on the patient of excessive blood loss is generally acknowledged. Earlier regimes of starvation and markedly restricted diet were aimed at providing a period of immobility of the upper digestive tract in the hope of promoting closure of the bleeding vessel. A more generous intake of food is now employed by most physicians in the hope of supporting the patient's strength during the bleeding period. No evidence has been produced that moderately high caloric intakes of bland foods aggravate the bleeding. On the other hand the expectations aroused in some that Meulengracht's [10] heavy and coarse diet would radically lower the death rate have not been fulfilled. Consideration of the pathology of fatal cases makes it evident that diet alone could not be expected to stop the arterial bleeding.

The former fear of replacing the loss in blood volume by transfusion of whole blood and plasma and by a more liberal fluid intake has largely disappeared. There is no doubt in the minds of those who have used these supportive measures freely that they are frequently life saving. Bennett and his associates [11] have made a valuable contribution to our knowledge of the indications for transfusion by following the levels of total plasma and total cell volumes in cases of recurrent bleeding from peptic ulcer.

The difficulty in predicting the outcome in the individual case either on the basis of clinical character of the bleeding, laboratory evidences of its extent, age of the patient, or knowledge of the site of the lesion is naturally a deterrent to early operative treatment. A further deterrent is the fact that surgical opinion generally favors resection as the operation of choice, a procedure which at best involves of itself a mortality rate of approximately 5 per cent. Unless performed early before the patient's condition has deteriorated, that is when the prognosis for spontaneous cure seems brightest, the mortality rate is prohibitive. On the average the percentage of fatalities after resection in massive hemorrhage is about the same as that shown by

[8] BULMER, E.: The mortality from haematemesis, Lancet, 1927, cxiii, 168.
[9] BULMER, E.: Mortality from haematemesis, Lancet, 1932, cxxiii, 720.
[10] MEULENGRACHT, E.: The medical treatment of peptic ulcer and its complications, Brit. Med. Jr., 1939, ii, 321.
[11] BENNETT, J. I., DOW, J., and WRIGHT, S.: Severe hemorrhage from stomach and duodenum, Lancet, 1942, cxliii, 550.

conservative treatment. The surgeon, however, deals with cases selected for severity.

It must be recalled also that upon exploring the abdomen the surgeon will not infrequently be unable by inspection or palpation to locate the point of bleeding. In this case he will be forced to choose between closing without accomplishment or performing a radical resection hoping to include the source of hemorrhage.[12] This situation is seldom discussed in recent surgical literature.

A conservative position at the present time is to restrict operation to patients in the older age groups; in whom available evidence indicates the presence of a chronic gastric or duodenal ulcer; who have bled dangerously once but not repeatedly; and have rallied before going on the table.

It is evident, however, that the decision for or against surgery in the individual case is a very difficult one and that the physician requires better methods than are now available for estimating in each instance the relative risks under conservative or surgical treatment.

In the face of the emergency created by active hemorrhage there is a tendency to underestimate the part played in the death rate of bleeding peptic ulcer by complications. Perforation occurring coincidently with hemorrhage is not uncommon and in the presence of shock may be readily overlooked. In Bulmer's [8, 9] 38 fatal cases of bleeding peptic ulcer in which postmortem examinations were made there were two instances of perforation. In Goldman's [13] 56 deaths, perforation had occurred in six. While the incidence reported by these two authors is unusually high, the possibility of perforation should be considered in all cases irrespective of age or extent of the hemorrhage. A further complication of hemorrhage especially in older people is the occurrence of cardiac damage evidenced by abnormal rhythms, frank congestive failure or cardiac infarction.[14] Cerebral thrombosis is not infrequently listed as a contributory cause of death. The lowered resistance of these patients may be held accountable for the frequent occurrence of lobar and bronchopneumonia. Parotitis is occasionally observed.

There is a known relationship between ulcer of the duodenum and chronic nephritis with uremia. Reports of gastroduodenal ulceration in association with hepatic cirrhosis are not uncommon. The coexistence of peptic ulcer and diabetes is not infrequently observed. In each of these instances the ulcer may bleed and the prognosis be aggravated because of the primary disease.

Relatively few authors have attempted to evaluate the part played by complications and by associated diseases in the death rate from bleeding peptic ulcer, but study of the scant number of autopsies reported makes it evident that this is an important aspect of the clinical problem.

[12] WANGENSTEEN, O. H.: The ulcer problem, Jr. Canad. Med. Assoc., 1945, liii, 309.
[13] GOLDMAN, L.: Gross hemorrhage from peptic ulcer, Jr. Am. Med. Assoc., 1936, cvii, 1537.
[14] KINNEY, T. D., and MALLORY, G. K.: Cardiac failure associated with acute anemia, New Eng. Med. Jr., 1945, ccxxxii, 215.

REVIEWS

Fundamentals of Clinical Neurology. By H. Houston Merritt, M.D., Professor of Clinical Neurology, College of Physicians and Surgeons, Columbia University; Chief of Division of Neuropsychiatry, The Montefiore Hospital; Fred A. Mettler, M.D., Ph.D., Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia University; and Tracy Jackson Putnam, M.D., Professor of Neurology and Neurological Surgery, College of Physicians and Surgeons, Columbia University. 289 pages; 25.5 × 17 cm. 1947. The Blakiston Company, Philadelphia. Price, $6.00.

The authors, who are outstanding leaders in the fields of clinical neurology, neuro-anatomy and neuro-surgery, have produced in this short (289 pages) monograph an excellently condensed review of the whole field of clinical neurology. It is full of excellent plates and diagrams which give function as well as location and name. The examination technics described in the first part of the book are especially useful because the positive findings of various tests are interpreted. The same applies to the description of spinal fluid examination. This book is in no sense an introductory book for beginners. Its main usefulness, as the reviewer sees it, will be for two groups: those who want a quick but complete review in preparation for American Board Examinations; and those medical practitioners who need assistance in the examination and understanding of the patients they encounter who have a disease of the nervous system.

H. W. N.

Digitalis and Other Cardiotonic Drugs. By Eli Rodin Movitt, M.D. 204 pages; 16 × 24.5 cm. Oxford University Press, New York. 1946.

Dr. Movitt has reviewed and abstracted the extensive recent literature pertaining to digitalis and related drugs. For the most part, the abstracts from original articles are detailed enough to convey clearly the author's view. Over 400 papers are analyzed in this monograph. There is fair presentation of opposing opinions on controversial subjects. The arrangement into chapters and the index facilitate ready reference.

The book will be of especial interest to cardiologists, but the general internist will find much of value. It will serve as a valuable reference to all workers in this field.

C. E. L.

BOOKS RECEIVED

Books received during July are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Advances in Internal Medicine (Volume II). Editors: William Dock, M.D., Long Island College of Medicine; I. Snapper, M.D., The Mount Sinai Hospital, New York. 642 pages; 24 × 16 cm. 1947. Interscience Publishers, Incorporated, New York. Price, $9.50.

Advances in Pediatrics (Volume II). Editorial Board: S. Z. Levine, Cornell University Medical College, New York; Allan M. Butler, Harvard Medical School, Boston; L. Emmett Holt, Jr., New York University, College of Medicine, New York; A. Ashley Weech, University of Cincinnati, College of Medicine, Cin-

cinnati. 409 pages; 24 × 16 cm. 1947. Interscience Publishers, Incorporated, New York. Price, $6.75.

Cancer: Diagnosis, Treatment, and Prognosis. By LAUREN V. ACKERMAN, M.D., Pathologist to the Ellis Fischel State Cancer Hospital, etc.; JUAN A. DEL REGATO, M.D., Radiotherapist to the Ellis Fischel State Cancer Hospital, etc. 1,115 pages; 25.5 × 18.5 cm. 1947. The C. V. Mosby Company, Saint Louis. Price, $20.00.

The Causation of Appendicitis. By A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S., Professor of Surgery, University of Bristol, etc. 79 pages; 19 × 12.5 cm. 1946. The Williams & Wilkins Company, Baltimore. Price, $2.50.

Concise Anatomy. By LINDEN F. EDWARDS, Ph.D., Professor of Anatomy, The Ohio State University, Columbus. 548 pages; 25.5 × 17.5 cm. 1947. The Blakiston Company, Philadelphia. Price, $5.50.

Dermatologic Clues to Internal Disease. By HOWARD T. BEHRMAN, M.D., Assistant Clinical Professor of Dermatology, New York University College of Medicine, etc. 165 pages; 23.5 × 16 cm. 1947. Grune & Stratton, Incorporated, New York. Price, $5.00.

Diseases Transmitted from Animals to Man (Third Edition). By THOMAS G. HULL, Ph.D., Director, The Scientific Exhibit, American Medical Association; and other contributors. 571 pages; 24.5 × 16 cm. 1947. Charles C. Thomas, Springfield, Illinois. Price, $10.50.

A Manual of Otology, Rhinology and Laryngology (Third Edition). By HOWARD CHARLES BALLENGER, M.D., F.A.C.S., Associate Professor and Acting Chairman of the Department of Otolaryngology, Northwestern University School of Medicine, Chicago, etc. 352 pages; 24 × 15.5 cm. 1947. Lea & Febiger, Philadelphia. Price, $4.50.

Medical Addenda: Related Essays on Medicine and the Changing Order. By Various Authors. 156 pages; 21.5 × 14 cm. 1947. The Commonwealth Fund, New York. Price, $1.75.

Medical Disorders of the Locomotor System, Including the Rheumatic Diseases. By ERNEST FLETCHER, M.A., M.D. (Cantab.), M.R.C.P., Physician to the Arthritis Clinic and Lecturer on the Rheumatic Diseases, Royal Free Hospital, etc. 625 pages; 25.5 × 16 cm. 1947. The Williams & Wilkins Company, Baltimore. Price, $11.00.

Ophthalmology, being Section XII of Excerpta Medica (A Complete Monthly Abstracting Service of the World Medical Literature Comprising 15 Sections and Covering the Whole Field of Theoretical and Clinical Medicine.) Under the General Editorship of M. W. WOERDEMAN, M.D., F.R.N.A.S., Professor of Anatomy and Embryology, University of Amsterdam, etc. 48 pages; 25 × 16.5 cm. (paper). 1947. The Williams & Wilkins Company, Baltimore. Price: Subscription, $15.00.

Osteotomy of the Long Bones. By HENRY MILCH, M.D., Consulting Orthopedist, Maimonides Hospital. 294 pages; 24 × 16 cm. 1947. Charles C. Thomas, Springfield, Illinois. Price, $6.75.

Physician's Handbook (Fourth Edition). By JOHN WARKENTIN, Ph.D., M.D., and JACK D. LANGE, M.S., M.D. 282 pages; 16.5 × 10 cm. (paper). 1946. University Medical Publishers, Chicago. Price, $1.50.

Signs and Symptoms: Their Clinical Interpretation. Edited by CYRIL MITCHELL MACBRYDE, A.B., M.D., F.A.C.P., Assistant Professor of Clinical Medicine, Washington University School of Medicine, etc. 439 pages; 26 × 18.5 cm. 1947. J. B. Lippincott Company, Philadelphia. Price, $12.00.

Skin Manifestations of Internal Disorders (Dermadromes). By KURT WIENER, M.D., Dermatologist, Mount Sinai Hospital, Deaconess Hospital, Saint Michael's Hospital, Milwaukee. 690 pages; 25.5 × 18 cm. 1947. The C. V. Mosby Company, Saint Louis. Price, $12.50.

The Years After Fifty. By WINGATE M. JOHNSON, M.D., Professor of Clinical Medicine and Chief of Private Diagnostic Clinic, Bowman Gray School of Wake Forest College. With a Foreword by MORRIS FISHBEIN, M.D., Editor, Journal of the American Medical Association. 153 pages; 21 × 14.5 cm. 1947. Whittlesey House, McGraw-Hill Book Company, Inc., New York. Price, $2.00.

The Development of Modern Medicine: An Interpretation of the Social and Scientific Factors Involved. By RICHARD HARRISON SHRYOCK. 472 pages; 22 × 15 cm. 1947. Alfred A. Knopf, Incorporated, New York. Price, $5.00. (Revised edition.)

COLLEGE NEWS NOTES

Research Fellowships—the American College of Physicians

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1948–June 30, 1949. The Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work.

The stipend will be from $2,200 to $3,000.

Application forms will be supplied on request to the American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than November 1, 1947. Announcement of the awards will be made as promptly as is possible.

Additional Life Members

The College takes great pleasure in announcing that the following Fellows, listed in the order of their subscriptions, have become Life Members of the College.

Stanley T. Simmons, Louisville, Ky., June 27, 1947
Louis F. Bishop, Jr., New York, N. Y., June 30, 1947
Ricardo Aguilar Meza, Tiquisate, Escuintla, Guatemala, July 8, 1947

Supplement to 1947 Membership Roster Distributed

A Supplement to the 1947 Membership Roster, designed to bring the membership list up to date as of August 1, 1947, has now been published and distributed to all members of the College in good standing. If any have failed to receive their copies, or have noted any corrections or omissions in the Supplement listings, they are requested so to inform the Executive Secretary of the College.

The Supplement records all elections at the 1947 Annual Session. It contains also the full Constitution and By-Laws, as amended on May 1 at the Session.

Twenty-Ninth Annual Session—San Francisco, Calif.

The 29th Annual Session of the College will be held in San Francisco, April 19–23, inclusive, 1948, with General Headquarters at the Civic Auditorium. No single hotel has adequate facilities to accommodate a large proportion of the members, but fully adequate hotel accommodations are available for everyone. The College will publish a list of "Official Hotels" and members may make reservations directly by identifying themselves with the College and with this meeting.

As President of the College, Dr. Hugh J. Morgan, Vanderbilt University Hospital, Nashville, Tenn., is responsible for the program of Morning Lectures and afternoon General Sessions. Dr. William J. Kerr and Dr. Ernest H. Falconer, of San Francisco, are Co-General Chairmen, and through them and their Committees, the pro-

Tentative Outline of San Francisco Session

Time	Monday April 19	Tuesday April 20	Wednesday April 21	Thursday April 22	Friday April 23
9:00 a.m. to 11:30 a.m.	Morning free. Registration, Exhibits, etc.	Hospital Clinics	* Morning Lectures (9:30–11:30)	Hospital Clinics	* Morning Lectures (9:30–11:30)
12:00 m. to 1:15 p.m.		Panel Discussions	Panel Discussions	Panel Discussions	Panel Discussions
1:15 p.m. to 2:15 p.m.	Luncheon	Luncheon	Luncheon	Luncheon	Luncheon
2:15 p.m. to 5:00 p.m.	1st General Session	2nd General Session	3rd General Session	Annual Business Meeting — 4th General Session	5th General Session
5:00 p.m. to 8:00 p.m.	Dinner		Dinner		
8:00 p.m. to 11:00 p.m.	Entertainment and Opening Reception		Convocation followed by President's Reception	Annual Banquet	

* Two simultaneous series.

gram of Clinics, Panel Discussions and Entertainment is being arranged. They have already appointed the following Committee Chairmen:

Dr. Dwight L. Wilbur, Committee on Clinics
Dr. Roberto F. Escamilla, Committee on Panel Discussions
Dr. Sidney J. Shipman, Committee on Entertainment
Dr. William C. Voorsanger, Committee on Hotels and Transportation
Mrs. Stacy R. Mettier, Committee on Ladies' Entertainment.

New features will be introduced into the program, among which will be a change in the organizational type of the Meeting. Hospital Clinics and Demonstrations will occupy exclusively two mornings, Tuesday and Thursday; there will be no conflicting Morning Lectures or other program features those two mornings. There will be two simultaneous programs of Morning Lectures on Wednesday and Friday mornings, without other conflicting program features. Panel Discussions, with several new ideas, will be conducted daily, Tuesday through Friday, from 12 m. to 1:15 p.m. The General Sessions will be held daily, Monday through Friday, from 2:15 p.m. to 5 p.m., but there will be no General Sessions in the evening.

It will be the 100th Anniversary of the "Gold Rush" and several unique features are being planned.

Autumn Schedule of Regional Meetings American College of Physicians

Territory	City	Date	General Chairman
Western Pennsylvania	Pittsburgh	September 10, 1947	R. R. Snowden, Governor
North Dakota	Bismarck	September 13, 1947	R. B. Radl, Governor
Oklahoma	Oklahoma City	September 20, 1947	Wann Langston, Governor
Nebraska	Lincoln	September 20, 1947	J. D. McCarthy, Governor
Iowa	Des Moines	September 27, 1947	B. F. Wolverton, Governor
New England (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island and Vermont)	Burlington, Vt.	October 14, 1947	Ellsworth L. Amidon, Governor
Western New York	Syracuse	October 28, 1947	E. C. Reifenstein, Sr., Governor
Western Michigan	Muskegon	October 29, 1947	W. M. LeFevre, Chairman
New Jersey	Newark	November 7, 1947	G. H. Lathrope, Governor A. J. V. Klein, Chairman
Kentucky	Louisville	November 8, 1947	C. W. Dowden, Governor
North Carolina	Chapel Hill	November 14, 1947	P. F. Whitaker, Governor R. L. McMillan, Chairman
Midwest (Illinois, Indiana, Michigan, Minnesota, Wisconsin)	Milwaukee	November 15, 1947	K. L. Puestow, Governor F. D. Murphy, Chairman
Eastern Pennsylvania and Delaware	Philadelphia	November 21, 1947	E. L. Bortz, Governor
Florida	Tampa	†December 8–9, 1947	T. Z. Cason, Governor W. C. Blake, Chairman

† Followed by a proposed trip to Havana where a Regional Meeting for Cuba will be conducted under Dr. José Centurión, Governor.

North Carolina Regional Meeting

The North Carolina Annual Regional Meeting of the American College of Physicians will be held at Chapel Hill, with the University of North Carolina Group acting as hosts, on Friday, November 14. Dr. Paul F. Whitaker, Kinston, is the Governor for North Carolina; Dr. Robert L. McMillan, Winston-Salem, is Chairman of the Program Committee; Dr. Edward McG. Hedgpeth, of Chapel Hill, is Chairman of Local Arrangements.

Fellows and Associates will be chosen very largely for program presentations, and it is predicted that this will be one of the largest and most enthusiastic meetings of the College ever held in North Carolina, which was one of the pioneer states in initiating regional meetings many years ago.

Postgraduate Courses by the American College of Physicians

In the advertising section of this issue of the Annals will be found the full schedule of courses offered by the American College of Physicians during the autumn of 1947. Already Course No. 1, Internal Medicine, has been concluded and Course

No. 2, Psychosomatic Medicine, at the University of Colorado, and Course No. 3, Mechanics of Disease, at the Peter Bent Brigham Hospital, Boston, are in progress. The Postgraduate Bulletin, together with detailed course outlines for Courses 1 to 5, were distributed to all Fellows and Associates of the College on August 1. In the meantime, the detailed outlines for the remaining courses have been received and printed and are available on request to the Executive Secretary of the College. The maximum facilities of these courses is 665. Many of the courses will be completely filled by members of the College while in some other courses, accommodations will be available for several qualified non-members.

The Advisory Committee on Postgraduate Courses has probably organized the most attractive postgraduate program this year in the history of the College, and through continued experience the courses improve in quality and grow in popularity.

University of California, Los Angeles, Offers Postgraduate Courses

"Lifelong Learning" is the title of a bulletin issued by the School of Medicine of the University of California, Los Angeles, listing Medical Refresher Courses scheduled between September and December, 1947. Courses are offered in Dermatology, Syphilology, Medical Mycology, Serology and Immunology; Gynecology; Otorhinolaryngology; Urology; Medicine; General Surgery; Cardiology; and Pediatrics. The courses will continue one evening per week from 8 p.m. to 10 p.m. over periods of approximately seven weeks, and the fee varies from $50.00 to $75.00, except the course in Pediatrics for which the fee is $25.00.

Chicago Medical Society Offers Postgraduate Courses

The Chicago Medical Society has announced a course in Cardiovascular Diseases, October 20–25, and a course in Gastro-enterology, October 27–November 1, each course limited to 100. The courses are open to all physicians in good standing in their county medical societies anywhere in the United States.

The Interstate Postgraduate Medical Association of North America will have its 1948 Assembly in Cleveland at the Public Auditorium during the week of November 8, 1948. Further information concerning the program of this Assembly will be published in a later issue.

Dr. Robert F. Loeb, F.A.C.P., New York, has been appointed Bard Professor of Medicine in the Columbia University College of Physicians and Surgeons, as well as Director of Medical Service in the Presbyterian Hospital. Dr. Loeb succeeds in this position Dr. Walter W. Palmer, President-elect of the College.

Dr. Lowell T. Coggeshall, F.A.C.P., Chicago, has been appointed to succeed Dr. R. Wendell Harrison as Dean of the Division of Biologic Sciences of the University of Chicago. This division includes the School of Medicine. Dr. Coggeshall also holds appointment as Professor of Medicine and Chairman of the Department.

Dr. Ross T. McIntire, F.A.C.P., Washington, D. C., formerly Surgeon General of the U. S. Navy, has been appointed Director of the American Red Cross' National Blood Program. In this position Dr. McIntire will supervise collection of an estimated 3,700,000 blood donations annually at strategically located centers throughout

the country. It is the purpose of the program to make available adequate supplies of whole blood and plasma and, in addition, the newer blood derivatives which have been developed largely during the war years. Such a program, conceived on a national scale, will utilize civic donor centers with mobile units to cover outlying communities. It is planned to utilize existing hospitals in the distribution of blood and blood fractions.

Dr. J. C. Geiger, F.A.C.P., San Francisco, Calif., has been honored by the award of the Gold Cross of the Royal Order of Phoenix by the Greek Government.

Dr. Peter J. Steincrohn, F.A.C.P., Hartford, Conn., has generously donated to the College Library of Publications by Members a copy of his new book, "What You Can Do for High Blood Pressure," published by Doubleday & Co., N. Y.

On September 1 Dr. Tom D. Spies, F.A.C.P., who has been Associate Professor of Medicine in the University of Cincinnati and has directed that University's nutritional investigations at the Hillman Hospital, Birmingham, Ala., will become Professor of Nutrition and Metabolism in the Northwestern University School. Northwestern University has created a new department in this field and Dr. Spies will have charge of it. He will continue his studies at the Hillman Hospital.

The Typhus Commission Medal has been awarded to Dr. Joseph F. Sadusk, Jr. (Associate), New Haven, Conn. This award recognizes Dr. Sadusk's important contributions to the study of scrub typhus while Executive Officer of the Special Commission in the Southwest Pacific in 1943.

Dr. Henry Pleasants, Jr., F.A.C.P., West Chester, Pa., has contributed to the College Library of Publications by Members a copy of his recent autobiographical book, "A Doctor in the House," which was published by J. B. Lippincott Co., Philadelphia.

Dr. R. E. Beamish (Associate) of the Manitoba Clinic, Winnipeg, Manitoba, Canada, has been awarded a Nuffield Foundation Traveling Fellowship for study in Great Britain and is now located in London.

Joint Committee for the Coördination of Medical Activities

The Joint Committee for the Coördination of Medical Activities, successor to the Committee on Post-War Planning for Medical Service, composed of representatives from the American Medical Association, the American College of Surgeons, the American Board for Medical Specialties, the American Dental Association, the American Hospital Association, American Pharmaceutical Association, Association of American Medical Colleges, the Veterans Administration, Office of the Surgeon General of the U. S. Army, the Bureau of Medicine and Surgery of the U. S. Navy, and several other organizations, is continuing its sessions during 1947, having held its last meeting at the A. M. A. Headquarters, on August 16, 1947. Among subjects on the agenda were:

Hospital Residencies and Graduate Education, by Dr. Donald Anderson;
Licensure, with particular reference to graduates of foreign extramural schools, by Dr. W. L. Bierring;

Report of the Subcommittee on a Specialty Board for General Practitioners;
Report of Subcommittee on Legislation for a National Department of Health;
Hospital Survey and Construction Program, by Miss Mary Switzer;
Shortage of Nursing Personnel, by Mr. Graham L. Davis;
Training of Practical Nurses, by Father Schwitalla;
New A. M. A. Committee on Nursing Problems;
The Navy Educational Program, by Capt. W. E. Eaton;
Rural Medical Service, by Dr. H. B. Mulholland;
A Progress Report on American Red Cross Blood Bank Program, by Dr. W. F. Draper.

Minutes of the Meeting will be published in the Journal of the American Medical Association.

Retirements from Service

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to July 14, 1947 inclusive).

Edward S. Brewster, Boone, Iowa (Lt. Col., MC, AUS)
Vincent Del Duca, Camden, N. J. (Capt., MC, AUS)
Robert E. Driscoll, Chicago, Ill. (Capt., MC, AUS)
George M. Edwards, Russellville, Ky. (Col., MC, USA)

OBITUARIES

DR. ALEXANDER W. WINKLER

Alexander W. Winkler, M.D., F.A.C.P., New Haven, Connecticut, died on June 26, 1947, at the age of 38.

Dr. Winkler was born November 20, 1908, in Ann Arbor, Mich. He received his B.A. degree from the University of Michigan in 1927 and his M.D. degree from Harvard Medical School, in 1931. Following an internship at Johns Hopkins Hospital he held a research fellowship at the Thorndike Memorial Laboratories, Harvard Medical School. In 1933 he came to New Haven, Conn., to become associated with the Yale University School of Medicine and the New Haven Hospital, advancing to the position of Assistant Professor of Medicine in 1941, which he held at the time of his death.

In addition to his work as an able clinician and teacher, Dr. Winkler had achieved distinction as an investigator in the fields of physiology and biochemistry as well as clinical medicine. The author of numerous scientific papers, his most notable contributions dealt with the metabolism of water and salts, diseases of the thyroid and diabetes.

He was a Fellow of the American Medical Association and a member of the American Society for Clinical Investigation, the American Diabetic Association, the American Physiological Society and the Interurban Clinical Club. He was also a member of three honorary societies: Phi Beta Kappa, Alpha Omega Alpha and Sigma Xi.

His death at an early age is a great loss to medicine.

FRANCIS G. BLAKE, M.D., F.A.C.P.

DR. ARCHIE MARVIN ROBERTS

Dr. Archie Marvin Roberts was born in Brandon, Texas, on August 2, 1902. He received his Bachelor of Arts degree at the University of Southern California in 1924, and graduated from Stanford University School of Medicine in 1929. After postgraduate study at Tulane University and Stanford Medical Schools, he entered private practice in Los Angeles in 1932. He was a diplomate of the American Board of Internal Medicine, 1938, became a Fellow of the American College of Physicians in 1942, and thereafter became a Life Member. He was a member of Stanford Chapter of the Society of Sigma Xi and Alpha Omega Alpha. He was a member of numerous local and national medical societies, and took an active part in all projects which would raise the standard of the practice of medicine in this area.

Dr. Roberts was Assistant Professor of Medicine at the University of Southern California Medical School, and had been President of the Los Angeles Heart Association from October, 1944, until the time of his death.

Dr. Roberts was a forceful member of many welfare organizations, and was a member of the Board of Directors of the Los Angeles County Tuberculosis Association. He was one of the most respected members of the medical profession in Southern California. His untimely death which took place suddenly on April 1, 1947, following an atypical pneumonia, was a great shock to all of his friends and colleagues.

LELAND HAWKINS, M.D., F.A.C.P.,
Governor for Southern California

DR. HAROLD FOSTER DUNLAP

The death of Dr. Harold Foster Dunlap, age 51, of Indianapolis, on July 22, 1947, is a great loss to the medical profession of Indiana. He was a highly trained physician in his special field of internal medicine and diagnosis.

Dr. Dunlap was born at Duncannon, Pa., the son of the Reverend Wilton and Irene (Beck) Dunlap. He received a Bachelor of Science degree at Indiana University in 1918, a Doctor of Medicine degree from the Indiana University School of Medicine in 1920, and a Master of Science in Medicine degree from the University of Minnesota in 1929. He served his internship at the Philadelphia General Hospital in 1920–22, and was a Fellow in Medicine at the Mayo Clinic, Rochester, Minn., in 1925, and a Consultant in Medicine there from 1925 to 1932. He was a diplomate of the American Board of Internal Medicine.

Dr. Dunlap was a member of the staffs of the Methodist, St. Vincent's and Indianapolis City Hospitals. He formerly was Chief of Medical Service at the City Hospital and served on many boards and committees of hospitals in Indianapolis. He had practiced in Indianapolis fourteen years, with an office at 723 Hume Mansur Bldg.

Dr. Dunlap was a member of the Lutheran Church, Phi Beta Pi Fraternity, the American Medical Association, the Association for Study of Internal Secretions, the Blockley Medical (Philadelphia) Alumni Association, the Mayo Foundation, and became a Fellow of the American College of Physicians in 1934. He was chairman of the medical advisory board of the Indiana Selective Service Commission and served on the Marion County Board of Appeals five years.

Dr. Dunlap's portrait is on file in the Army Medical Library, Washington, D. C., as a person prominent in the field of medicine.

ROBERT M. MOORE, M.D., F.A.C.P.,
Governor for Indiana